

ORIGINAL ARTICLE

Adverse reactions and alleged allergy to local anesthetics: Analysis of 331 patients

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ABSTRACT

The aim of this study was to determine the prevalence of true local anesthetic (LA) allergy among patients referred for suspected hypersensitivity and to describe the main characteristics of adverse drug reactions (ADR) induced by LA in our population. We retrospectively analyzed the medical files of patients referred to the Department of Dermatovenereology, University Hospital Center Rijeka, Rijeka, Croatia, for the investigation of LA hypersensitivity in the period between January 2000 and December 2012. A total of 331 patients underwent skin testing and, in cases of negative results, subcutaneous exposition to LA. In patients with suspected delayed reaction, patch test was performed. Altogether, 331 patients reported 419 independent ADR occurring during 346 procedures. Most commonly, patients reported having only one ADR, but 41 (12.4%) of them had two reactions, 14 (4.2%) had three, five (1.5%) had four and in one patient (0.3%) five ADR to LA were observed. The majority of reactions occurred during dental procedures when most commonly lidocaine and articaine were used. Local reactions were reported in 44 patients, whereas 490 general symptoms occurred during 375 independent ADR in 287 patients. The most common symptoms were cardiovascular system reactions in 89 patients (18.2%). Allergic reaction was detected in three patients (0.91%). One patient showed immediate-type reaction to bupivacaine and two patients had a delayed-type reaction to lidocaine. Adverse reactions to LA are common and are mostly due to their pharmacological properties and drug combinations or psychogenic origin. Allergic accidents to LA are rare.

Key words: adverse drug reaction, allergic reaction, drug hypersensitivity, drug provocation test, local anesthetics.

INTRODUCTION

Local anesthetic (LA) agents have been extensively used since the late 19th century and are the most commonly used drugs in everyday practice and in many branches of medicine, especially dentistry, minor surgery, urology, dermatology, obstetric procedures and orthopedics.

Adverse reactions to LA are frequently reported by patients.^{1–7} Most of these reactions are not immune mediated, and true immune-mediated reactions are considered extremely rare and are estimated to account for less than 1% of all adverse reactions to LA.^{2–6} According to the World Health Organization, an adverse drug reaction (ADR) is defined as any noxious and unintended effect related to drug administration in recommended doses, regardless of the route of administration.⁸

Suspected ADR lead to unnecessary drug avoidance by patients or even medical practitioners during medical procedures and treatments. Generally, in everyday practice most of

the patients experiencing any type of reaction following LA application are labeled “allergic”, although the reactions are generally of pharmacological, toxic, pseudo-allergic, autoimmune or other origin. The term “drug allergy” should be restricted to patients with a proven immunological cause.⁹ According to the responsible immunological pathomechanisms involved as well as the onset of symptoms, an immune-mediated reaction could be type IV, a T-cell-mediated or an immediate immunoglobulin E-mediated reaction. Type IV reactions were considered more common,^{1,5,6,10–13} but some authors have recently suggested immediate-type allergies to be more common.¹⁴ A delayed type IV hypersensitivity to LA is mainly related to ester-LA resulting in contact allergy of skin or mucosa, or potential allergic reactions to preservatives.^{3,12,13}

The aim of this study was to determine the prevalence of true LA allergy among the patients referred for suspected hypersensitivity and to describe the main characteristics of ADR following the application of LA in patients tested.

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METHODS

The study protocol was approved by the local ethics committee according to the World Medical Association guidelines outlined in the Declaration of Helsinki. All patients referred to the Department of Dermatovenereology, Clinical Hospital Center Rijeka, Rijeka, Croatia, for the investigation of LA hypersensitivity in the period between January 2000 and December 2012 were included in this study. We retrospectively analyzed the medical files of all patients referred to our department by their general practitioners, dentists and other specialists because of previous suspected allergic reactions to LA.

Informed written consent was obtained from all patients, and they were hospitalized at our department for extensive clinical work-up. Information regarding circumstances of occurrence of an adverse reaction following LA administration, a description of the reaction, its onset and duration, type of medical procedure undertaken, whether a known type of LA was used and complete personal history, especially disorders suggesting atopic diathesis, was especially important.

Antihistamines were stopped at least 1 week and oral corticosteroids at least 1 month prior to skin tests. Antihypertensive therapy with beta-blockers and angiotensin-converting enzyme inhibitors as well antidepressive therapy with antihistamine side-effects were switched over to alternative regimens before testing.

All patients underwent skin testing including scratch test, skin prick test (SPT) and intradermal test (IDT) followed by subcutaneous exposition test (SCT)^{7,14–16} to at least one preservative-free LA solution, most commonly one of the following: 2% lidocaine hydrochloride (LIDOKAIN 2% injection; Belupo, Koprivnica, Croatia), 0.5% bupivacaine hydrochloride (Marcaïne 0.5% solution for injection; AstraZeneca, Södertälje, Sweden) and 0.5% levobupivacaine hydrochloride (Chirocaine 5 mg/mL solution for injection; Abbot, Campoverde Di Aprilia, Italy). Diagnostic procedure started with scratch test in dilutions of 1:1000, 1:100 and 1:10 with positive (histamine chloride 1 mg/mL) and negative (0.9% sodium chloride) control on the anterior side of a patient's forearms. SPT was performed in case of negative scratch test with the same dilutions, followed by IDT.

All skin tests, scratch test, SPT and IDT, were evaluated after 20 min and after 24 h. The positivity of skin test was established when mean wheal diameter was at least 3 mm more for SPT and at least 10 mm more for IDT, and in case of clear wheal and flare reaction in scratch test according to European Academy of Allergology and Clinical Immunology (EACCI) and European Society of Contact Dermatitis guidelines.^{1,15–19} In cases of suspected delayed reaction, patch tests were performed using 5%, 15% and 30% drug dilution in petrolatum and pure liquid drug on Finn Chamber (Epitest, Tuusula, Finland) or on Scanpor (Alpharma, Oslo, Norway), read after 48 and 72 h, and graded according to International Contact Dermatitis Research Group guidelines and international standards.^{14,17,20,21} In patients with negative skin testing drug provocation tests (DPT) were performed, and they received increasing subcutaneous doses up to a therapeutic dose of 1 mL at the lateral surface of patients' arms as recommended

by the EACCI and recent guidelines.^{7,15–17} All DPT patients were blinded and preceded by a controlled challenge with placebo (0.9% saline).

Patients challenged with two or more LA, received an incremental dose of a single drug up to a therapeutic dose on the first day until a reaction occurred; if not, DPT was continued with the next LA the following day. All patients were observed and hospitalized for at least 48 h after the challenge, as well as followed up for the next 7 days.

Statistical analysis of the data was carried out in the program Statistica ver. 9.0 (StatSoft, Tulsa, OK, USA). χ^2 -Tests were used for calculating statistical significances of categorical data. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 331 patients were included in this study. The age range was 8–88 years, the median age being 50 years. ADR occurred more frequently in women (258 patients, 78%) than in men (73 patients, 22%) ($P < 0.001$). Altogether, 331 patients reported 419 independent ADR occurring during 346 procedures. Most commonly, patients reported having only one ADR (270 patients, 81.6%), but 41 (12.4%) of them had two reactions; 14 patients (4.2%) had three ADR, five patients (1.5%) had four, and in one patient (0.3%), five ADR to local anesthetics were observed.

Patients experiencing ADR reported different symptoms that were classified as local and systemic or general. Local symptoms were classified as erythema or edema occurring at the site of application or manifesting at different parts of the face. On the other hand, general symptoms reported varied from anaphylactic reaction to itch. Local symptoms were reported in 44 cases, whereas altogether 490 general symptoms occurred during 375 independent ADR in 287 patients. Tables 1 and 2 summarize general and local symptoms reported during ADR as well as used treatment with regard to symptoms. Generally, ADR resolved spontaneously and required no treatment. According to the patients' histories, therapy was applied in 116 patients that reported altogether 176 general (35.9%) and 14 local symptoms (31.81%). Treatment mainly consisted of antihistamines and corticosteroids that resulted in fast resolution of symptoms, whereas only in six cases of reported anaphylactic reaction epinephrine had been used.

Out of 419 reported ADR to LA, the majority of reactions occurred during dental procedures, followed by minor surgery interventions, intra-articular interventions, skin surgery procedures, regional anesthesia and ocular procedures, as shown in Table 3.

According to the patients' histories, the most commonly used LA resulting in ADR were lidocaine and articaine. Lidocaine was used in 17 cases (38.6%) of local and 114 cases (30.4%) of systemic ADR, either alone or in combination with epinephrine or corticosteroids. In 110 ADR, the LA used was unknown. Table 4 presents the distribution of different LA used during procedures resulting in local or general ADR.

Adverse drug reactions to LA were more common in patients reporting an ADR to some other drug ($P < 0.05$). Out

Table 1. Reported systemic symptoms manifested during adverse drug reactions (ADR) and required treatment

Systemic symptoms during ADR	No. (%)	Treated, n (%)	Not treated, n (%)
Generalized weakness	85 (17.3)	8 (9.4)	77 (90.6)
Hypertension, hypotension	51 (10.4)	0 (0)	51 (100)
Itch	50 (10.2)	24 (48)	26 (52)
Dyspnea, bronchospasm	50 (10.2)	21 (42)	26 (58)
Rash	45 (9.2)	31 (68.9)	14 (31.1)
Dizziness	43 (8.8)	2 (4.7)	41 (95.3)
Palpitations, arrhythmia, tachycardia	38 (7.8)	9 (23.7)	29 (76.3)
Fainting, syncope	35 (7.1)	14 (40)	21 (60)
Angioedema	29 (5.9)	27 (93.1)	2 (6.9)
Fear, sweating	26 (5.3)	5 (19.2)	21 (80.8)
Urticaria	19 (3.9)	18 (94.7)	1 (5.3)
Nausea, vomitus, diarrhea	13 (2.7)	1 (7.7)	12 (92.3)
Anaphylactic shock	6 (1.2)	6 (100)	0 (0)
Total ^{†,‡}	490 (100)	176	314

[†]Different symptoms occurring simultaneously during an ADR event were counted separately.

[‡]Reported cases of anaphylactic shock were treated with epinephrine while all other systemic symptoms were treated with antihistamines and/or corticosteroids.

Table 2. Reported local symptoms manifested during adverse drug reactions (ADR) and required treatment

Local symptoms during ADR	No. (%)	Treated, n (%)	Not treated, n (%)
Erythema of face and neck	17 (38.6)	1 (5.9)	16 (94.1)
Edema of face and cheeks	16 (36.4)	6 (37.5)	10 (62.5)
Edema of lips and tongue	8 (18.2)	7 (87.5)	1 (12.5)
Local edema (site of local anesthetic application)	3 (6.8)	0 (0)	3 (100)
Total ^{†,‡}	44 (100)	14	30

[†]Different symptoms occurring simultaneously during an ADR event were counted separately.

[‡]All local symptoms were treated with antihistamines and/or corticosteroids.

Table 3. Reported adverse drug reactions (ADR) regarding type of procedure

Type of procedures	ADR, n (%)
Dental procedures	308 (73.5)
Minor surgery procedures	55 (13.1)
Intra-articular procedures	37 (8.8)
Skin surgery	13 (3.1)
Regional anesthesia	4 (1)
Ocular interventions	2 (0.5)
Total	419 (100)

of 331 patients who reported ADR to LA, 146 patients (44.10%) reported ADR to some other drug, most commonly penicillin (71/146, 48.63%), other antibiotics (67/146, 45.89%),

Table 4. Adverse drug reactions (ADR) regarding to local anesthetic used

Local anesthetic	Local ADR, n (%)	Systemic ADR, n (%)
Lidocaine	3 (6.8)	43 (11.5)
Lidocaine + epinephrine	6 (13.6)	59 (15.7)
Lidocaine + betamethasone	8 (18.2)	12 (3.2)
Mepivacaine	1 (2.3)	14 (3.7)
Articaine	13 (29.5)	86 (22.9)
Bupivacaine	5 (11.4)	29 (7.7)
Procaine	1 (2.3)	27 (7.2)
Benzocaine gel	0 (0)	1 (0.3)
Tetracaine	1 (2.3)	0 (0)
Unknown	6 (13.6)	104 (27.8)
Total	44 (100)	375 (100)

non-steroidal anti-inflammatory drugs (63/146, 43.15%), acetylsalicylic acid (28/146, 19.17%) and other drugs (36/146, 24.65%). Multi-drug reaction was reported in 90 (27.19%) patients.

Excluding other drug allergies, associated allergic conditions such as asthma, atopic dermatitis, allergic rhinitis or food allergy were found to be more common in patients who reported ADR to LA (114/331, 34.44%; $P < 0.05$).

Adverse drug reactions to LA were more common in patients who had some associated illness compared with the patients who did not report any disease ($P < 0.001$). Out of 331 patients examined, 254 (76.74%) reported some associated illness and 99 (29.91%) reported more than one illness. The most common were cardiovascular diseases (122/254, 48.03%), followed by liver disease (31/254, 12.20%), autoimmune diseases (25/254, 9.8%), malignant neoplasm (23/254, 9.05%), thyroid disease (16/254, 6.3%), diabetes mellitus (10/254, 3.94%), psychiatric illnesses (7/254, 2.76%) and epilepsy (1/254, 0.39%), while other diseases were reported in 149 (58.66%) patients.

According to the patients' histories, the majority of adverse reactions manifested within the first hour following LA application (232 patients, 70.1%). Reported onsets of ADR following LA application are shown in Table 5.

Out of 331 patients who underwent skin testing, allergic reaction was detected in only three patients (0.91%). A 30-year-old male patient exhibited immediate type I reaction

Table 5. Onset of adverse drug reactions (ADR) following local anesthetic application

Time of ADR onset	Patients, n (%)
<5 min	60 (18.1)
5–30 min	96 (29)
30–60 min	76 (23)
1–6 h	52 (15.7)
6–24 h	28 (8.46)
>24 h	19 (5.74)
Total	331 (100)

during IDT to bupivacaine. He reported a local edema on the treated side of the face and generalized urticaria developing within 15 min following an unknown LA application. The patient was taking therapy for epilepsy and reported having ADR to different non-steroidal anti-inflammatory drugs. Because IDT to bupivacaine was clearly positive, we did not continue with subcutaneous challenge. Instead, complete skin test protocol, as well as subcutaneous exposition to lidocaine and levobupivacaine, was successfully completed and determined lidocaine and levobupivacaine as safe alternatives. Allergy examination was performed 1 year after the adverse reaction took place.

Patch testing was performed in 110 of 331 patients (33.23%) and only two female patients tested positive for type IV reaction to lidocaine. Complete skin test protocol, as well as subcutaneous exposition to bupivacaine and levobupivacaine, was negative in both cases. In a 38-year-old female patient, patch testing was performed 1 year following adverse reaction. She reported no associated illnesses or allergies, except a delayed occurrence of local facial edema and urticaria 20 h following LA application because of dental procedure. In a 72-year-old female patient, examination was performed more than 15 years following the reaction. She reported dizziness immediately after lidocaine spray application, followed by pruritus and exanthema 5–6 h later. She was under treatment for hypothyreosis, hypertension and depression and was operated for gynecological malignant disease that was considered completely cured after 15 years.

Altogether, 32 patients reported different symptoms occurring after exposition to placebo that were, generally, similar to the symptoms of original ADR and are summarized in Table 6. Patients reacting to placebo reported no reaction following the application of suspected LA whatsoever. Also, in all 32 patients, a safe, alternative LA was determined.

In 134 patients (40.5%), ADR were recent events occurring within the last 6 months, while in 202 patients (61%), ADR occurred within the year preceding examination. The distribution of patients according to time difference between ADR and testing is summarized in Table 7.

Table 6. Reported symptoms in patients reacting to placebo testing

Symptoms in patients reacting to placebo	No. (%)
Dyspnea, bronchospasm	14 (22.2)
Fainting, syncope, dizziness	13 (20.7)
Generalized weakness	13 (20.7)
Palpitations, arrhythmia, tachycardia	6 (9.5)
Facial flushing	4 (6.3)
Hypertension, hypotension	4 (6.3)
Fear, sweating	4 (6.3)
Nausea, vomitus, diarrhea	3 (4.8)
Itch	2 (3.2)
Total†	63 (100)

†Different symptoms occurring simultaneously during a reaction to placebo were counted separately.

Table 7. Time elapsed between adverse drug reactions (ADR) to local anesthetic and testing

Time elapsed between ADR and testing	Patients, <i>n</i> (%)
<1 month	28 (8.5)
1–3 months	60 (18.1)
3–6 months	46 (13.9)
6–12 months	68 (20.5)
1–5 years	37 (11.2)
5–10 years	33 (10)
10–20 years	31 (9.3)
>20 years	28 (8.5)
Total	331 (100)

DISCUSSION

Adverse reactions to LA are frequently reported by patients. Although most of these reactions are not immune mediated and generally involve vasovagal or anxiety reaction, pharmacological properties of LA or combinations used, toxic effects due to large doses or mistaken intravascular injection, many patients are referred to allergy clinics and undergo extensive evaluation in order to exclude a true immune-mediated reaction.^{1–7}

Adverse drug reactions to LA were found to be more common in women than in men and generally occurred in middle-aged patients as previously observed by some authors.^{3,4,7,14,22} On the other hand, some studies found no difference in the occurrence of ADR according to sex^{23–25} or found the incidence was more common in men.²⁶

Adverse drug reactions involve many systems and organs manifesting with a wide range of symptoms manifesting as general or local reactions. As suggested earlier,^{27,28} the most common systemic symptom was cardiovascular system reaction, which manifested as palpitation, cardiac arrhythmia, tachycardia, hypotension or hypertension in 89 patients (18.2%). These symptoms could be a result of LA systemic toxicity due to high plasma levels of LA because of accidental intravascular injection, high LA dosage, personal susceptibility or associated illnesses.^{23,29} Myocardial disease could decrease personal tolerance to LA, leading to increased possibilities of adverse reactions. Also, other reported associated illnesses, such as liver disease, thyroid disease and diabetes, could influence a patient's tolerance to LA or alter pharmacokinetics and distribution of LA.^{12,23,29,30}

Most of the ADR reported were mild in nature, manifested within 30 min or 1 h following LA application and regressed spontaneously without any treatment, as reported previously.^{3,4,23} These symptoms were mainly due to neurovegetative and psychogenic reactions.

Adverse drug reactions to LA occurred most commonly during dental procedures and other minor surgery procedures. Our patients were usually referred by their dentists in the need for a safe LA to use following their history of previous adverse reactions, as reported previously.^{4,7,23}

According to the patients' histories, the most commonly used LA were of the amide group, including lidocaine, articaine

and bupivacaine, whereas LA of the ester group, such as procaine, benzocaine and tetracaine, were less commonly used, as reported previously.^{3,4,23,27} Because the study was retrospective, we could not obtain complete information about LA used in all ADR. Amide LA are transferred to the liver and metabolized by microsomal enzymes, so decreased liver function could lead to more common adverse reactions.^{12,30} On the other hand, esters are metabolized rapidly by plasma pseudo-cholinesterase and altered enzyme function could result in increased adverse reactions.³⁰

Incidence of ADR to LA has been shown to be much higher in case of combination drug, especially epinephrine, a most commonly added combination drug.²³ Epinephrine prolongs the anesthetic effect of LA, reducing the removal of LA from an injection site due to vasoconstriction of vessels, and can cause hypertension.^{28,31} Adrenergic reactions are often misdiagnosed as allergic reactions. Patients with some associated illnesses, such as thyroid diseases, have been suggested to be more sensitive to epinephrine. Unfortunately, as a large proportion of the patients could not identify the drug used, the real significance of epinephrine as a contributing factor to ADR could not be clearly determined.

Psychological stress and fear of procedure itself or LA injection could result in psychogenic symptoms and contribute to the development of symptoms from other organ systems.^{7,22} It has been suggested that psychogenic stress can alter blood levels of stress hormones and increase sympathetic activation, influencing heart rate and sensitivity to pain.³² Psychogenic reactions could have contributed to symptoms reported by 32 patients following placebo application and mainly consisted of general weakness, altered heart rate, dizziness or fainting, fear and anxiety. Reported symptoms, surprisingly, required no therapeutic intervention or, regressed following s.c. or i.v. application of 0.9% saline. These patients could be considered as having had inconclusive test results. Even though there was no adverse reaction to suspected LA, these patients were advised to avoid previously used LA for security reasons and alternative LA were recommended for further use.

Although allergic reactions to LA are extremely rare,²⁻⁶ a recent study suggested the necessity of intradermal testing to LA in patients with a history of an allergic condition.²³ According to the patients' histories and self-assessments, 34.4% reported having at least one allergic condition, whereas 44.10% of patients reported having ADR to other drugs. In cases of reported multi-drug reactions, most commonly suspected drugs were antibiotics, especially penicillin, followed by aspirin and non-steroidal anti-inflammatory drugs.⁷

It is important to note that in some cases allergy testing was performed retrospectively, in some cases even more than 20–30 years following an adverse reaction to LA. In the majority of patients, testing was performed in the first few months to 1 year following the reaction. Because the extent of sensitization to a drug decreases over time, the conduction of drug provocation testing after a long period of time can result in an increased number of negative results.¹⁷ Although the extent of sensitization decreases over time, allergy testing performed in a 72-year-old female more than 15 years following the reaction

detected a type IV positive reaction to lidocaine but no type I and type IV reactions to bupivacaine and levobupivacaine, as safe alternatives.

Because safe alternatives were determined in all three cases of confirmed allergic reaction and there was a possibility of "resensitization" induction with each new course of therapy, the patients were not retested a few days later in order to determine a possible development of positive reaction due to boosting effect.³³ No cross-reactions with other amide LA were found, confirming it to be a rare event.^{4,6} In the majority of examined patients, the further use of a previously suspected LA and/or other safe alternative could be recommended for common local interventions in a therapeutic dose.

Generalized urticaria is, mainly, due to immediate reaction, as was the case in a male patient who exhibited type I reaction during IDT to bupivacaine. A delayed occurrence of urticaria and edema following s.c. LA application can be related to a type IV T-cell-mediated reaction,³⁴ like in our 38-year-old female patient. Although a delayed type IV hypersensitivity to LA is mainly related to ester-LA, resulting in contact allergy of skin or mucosa, or a potential allergic reaction to preservatives,^{3,12,13} we have detected a type IV allergic reaction to amide-type LA lidocaine in two patients.

Adverse drug reactions to LA are common and are mostly due to their pharmacological properties and drug combinations or psychogenic origin. There is a possibility of toxic effects due to overdose or intravascular injection. However, allergic reactions to LA account for less than 1% of ADR and are more commonly type IV immune reactions. Skin tests and drug challenge test offer a reliable method for exploring allergies in order to confirm or rule out immediate or delayed allergy to LA. We consider LA safe drugs to be used if needed.

REFERENCES

- Thyssen JP, Menne T, Elberling J, Plaschke P, Duus Johansen J. Hypersensitivity to local anesthetics – update and proposal of evaluation algorithm. *Contact Dermatitis* 2008; **59**: 69–78.
- Fisher MM, Bowey CJ. Alleged allergy to local anesthetics. *Anaesth Intensive Care* 1997; **25**: 611–614.
- Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996; **97**: 933–937.
- Baluga JC, Casamayou R, Carozzi E *et al.* Allergy to local anesthetics in dentistry. Myth or reality? *Allergol Immunopathol* 2002; **30**(1): 14–19.
- Noormalin A, Shahnaz M, Rosmilah M, Mujahid SH, Gendeh BS. IgE-mediated hypersensitivity reaction to lignocaine – a case report. *Trop Biomed* 2005; **22**(2): 179–183.
- 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. *J Invest Allergol Clin Immunol* 2006; **16**(5): 311–313.
- Wohrl S, Vigl K, Stingl G. Patients with drug reactions – is it worth testing. *Allergy* 2006; **61**: 928–934.
- Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**: 1255–1259.
- Johansson SGO, Bieber T, Dahl R *et al.* Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organisation, October 2003. *J Allergy Clin Immunol* 2004; **113**(5): 832–836.

- 10 Berkun Y, Ben-Zvi A, Levy Y, Galili D, Shalit M. Evaluation of adverse reactions to local anesthetics: experience with 236 patients. *Ann Allergy Asthma Immunol* 2003; **91**: 342–345.
- 11 Prieto A, Herrero T, Rubio M *et al*. Urticaria due to mepivacaine with tolerance to lidocaine and bupivacaine. *Allergy* 2005; **60**: 2612.
- 12 Lukawska J, Rosario Caballero M, Tsabouri M, Dugue P. Hypersensitivity to local anesthetics – 6 facts and 7 myths. *Clin Immunol Curr Allergy* 2009; **22**(3): 117–120.
- 13 Armado A, Sood A, Taylor J. Contact allergy to lidocaine: a report of sixteen cases. *Dermatitis* 2007; **18**: 215–220.
- 14 Fuzier R, Lapeyre-Mestre M, Mertes PM *et al*. Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing. *Pharmacoevidemiol Drug Saf* 2009; **18**: 595–601.
- 15 Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; **7**: 45–51.
- 16 Aberer W, Bircher A, Romano A *et al*. European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; **58**: 854–863.
- 17 Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Derm* 2001; **45**: 321–328.
- 18 Demoly P, Bousquet J. Drug allergy diagnosis work up. *Allergy* 2002; **57** (Suppl 72): 37–40.
- 19 Osterballe M, Scheller R, Stahl Skov P, Andersen KE, Bindslev-Jensen C. Diagnostic value of scratch-chamber test, skin prick test, histamine release and specific IgE in birch-allergic patients with oral allergy syndrome to apple. *Allergy* 2003; **58**: 950–953.
- 20 Bourke J, Coulson I, English J. Guidelines for the management of contact dermatitis: an update. *Br J Dermatol* 2009; **160**: 946–954.
- 21 Wahlberg JE, Lindberg M. Patch testing. In: Frosch PJ, Menne T, Lepoittevin JP, eds. *Contact Dermatitis*. Heidelberg: Springer, 2006; 366–386.
- 22 Berrino AM, Voltolini S, Bignardi D *et al*. Psychological aspects of drug intolerance. *Eur Ann Allergy Clin Immunol* 2005; **37**(3): 90–95.
- 23 Liu W, Yang X, Li C, Mo A. Adverse drug reactions to local anesthetics: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* Published online: 5 September 2013; **115**(3): 319–327.
- 24 Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol* 2001; **2**(6): 349–351.
- 25 Tofoli GR, Ramacciato JC, Volpato MC, Meechan JG, Ranali J, Groppo FC. Anesthetic efficacy and pain induced by dental anesthesia: the influence of gender and menstrual cycle. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**(2): e34–e38.
- 26 Kaufman E, Goharian S, Katz Y. Adverse reaction triggered by dental local anesthetics: a clinical survey. *Anesth Prog* 2000; **47**: 134–138.
- 27 Fuzier R, Lapeyre-Mestre M, Samii K, Montastruc JL, French Association of Regional Pharmacovigilance Centre. Adverse drug reactions to local anesthetics: a review of the French pharmacovigilance database. *Drug Saf* 2009; **32**: 345–356.
- 28 Bader JD, Bonito AJ, Shugars DA. A systematic review of cardiovascular effects of epinephrine on hypertensive dental patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 647–653.
- 29 Lustig JP, Zusman SP. Immediate complications of local anesthetic administered to 1007 consecutive patients. *J Am Dent Assoc* 1999; **130**: 496–499.
- 30 Subramaniam S, Tennant M. A concise review of the basic biology and pharmacology of local analgesia. *Aust Dent J Mediat Supp* 2005; **50** (Suppl 2): s23–s30.
- 31 Rizzi MD, Weil RJ, Lorenz RR. Severe transient hypertension after greater palatine foramen block in a patient taking midodrine. *Am J Otolaryngol* 2010; **31**: 67–69.
- 32 Montebugnoli L, Servidio D, Miaton RA, Prati C. Heart rate variability: a sensitive parameter for detecting abnormal cardiocirculatory changes during a stressful dental procedure. *J Am Dent Assoc* 2004; **135**: 1718–1723.
- 33 Torres MJ, Blanca M, Fernandez J *et al*. Diagnosis of immediate allergy to beta-lactam antibiotics. *Allergy* 2003; **58**: 961–972.
- 34 Orasch CE, Helbling A, Zanni MP, Yawalkar N, Hari Y, Pichler WJ. T-cell reaction to local anesthetics: relationship to angioedema and urticaria after subcutaneous application-patch testing and LTT in patients with adverse reactions to local anesthetics. *Clin Exp Allergy* 1999; **29**: 1549–1554.