

Long-term absence of sensitization to mepivacaine as assessed by a diagnostic protocol including patch testing

C. ASTARITA, D. GARGANO, C. ROMANO, M. CUTAJAR, F. MANGUSO*, D. MONTANARO, A. NAPOLITANO, F. PEZZUTO†, M. LO SCHIAVO†, P. ALTUCCI and G. ABBATE

Section of Allergology and Clinical Immunology, Division of Internal Medicine, 'F. Magrassi' Department of Clinical and Experimental Medicine, Second University of Naples School of Medicine, *Graduate Programme in Digestive and Nutritional Physiopathology, 'Federico II' University School of Medicine, Naples, and †Allergy Unit, ASL SA2, Salerno, Italy

Summary

Background Prospective assessment of non-reactivity to local anaesthetics is a frequent reason for allergy consultation.

Objectives To investigate the clinical profiles of subjects referred for allergy evaluation; to prospectively reduce the frequency of evaluation by assessing the persistence, during clinical use, of non-reactivity to contaminant/additive-free mepivacaine; and to determine the usefulness of a diagnostic protocol involving patch testing.

Methods In a prospective study, 198 consecutive patients underwent collection of clinical data, skin prick tests and patch tests using allergens/antigens relevant for the investigation, and an intradermal/subcutaneous challenge procedure using contaminant/additive-free mepivacaine, as appropriate. Patients were followed up for 3 years for assessment of non-reactivity persistence using the same diagnostic protocol.

Results Only one-third of the patients had a history of previous adverse local anaesthetic reactions. Absence of sensitization to contaminant/additive-free mepivacaine persisted in all subjects completing the follow-up. Controlled challenge with mepivacaine was negative in 196 patients with both negative specific skin prick tests and patch tests but it was eventful in two subjects with positive specific patch tests. A few subjects displayed positive skin prick tests and/or patch tests for latex and/or additives.

Conclusions A few patients had a relevant history for potential local anaesthetic-induced adverse reactions. Upon assessment of absence of sensitization and reactivity, contaminant/additive-free mepivacaine could safely be given for as long as 3 years. The patch testing was shown to be useful and safe for prediction of challenge outcomes. True allergic reactions to contaminant/additive-free mepivacaine were not observed in our patient series.

Keywords: adverse drug reactions, local anaesthetics, long-term non-reactivity, mepivacaine, patch tests

Clinical and Experimental Allergy, Vol. 31, pp. 1762–1770. Submitted 19 December 2000; revised 30 April 2001; accepted 11 May 2001.

Introduction

Although local anaesthetics (LAs) are relatively good

sensitisers when applied topically, adverse LA-induced reactions (ALARs) by IgE-mediated allergic mechanisms are rare [1–5]. ALARs, regardless of the inducing pathogenic mechanism, are a compelling problem, especially in dentistry [4–8], as 2.5–10% of patients treated in

Correspondence: Corrado Astarita, Via Vittorio Veneto 3, 80067 Sorrento (NA), Italy. E-mail: astcor@sorrento.argosid.it

general dental practice experience ALARs with a rate that is reportedly 10 times higher than that in medicine for the same drugs [9]. Because nearly 2 million injections of LAs are given every day [9], alleged ALARs are a frequent reason for allergy consultation. Indeed, it is our everyday experience to deal with patients who are referred, for fear of medical legal problems by their dentists/physicians, for allergy work-up to make sure that impending exposure to LAs is safe, even though a defined history of previous ALARs is often lacking. A number of these patients, moreover, are referred for frequent, even annual, consultations, because of repeated use of LAs. In terms of figures, the percentage of subjects referred to our Allergy Section for LA reactivity assessment has increased from 4.5% in 1992–93 to 8.5% in 1996–97, of which the percentage of new patients referred for the first time for assessing LA reactivity was 4% and 6.5% during the same time periods, respectively.

Indeed, true allergic reactions to LAs are documented [4,11,12], therefore skin prick testing (SPT) and eventually a subsequent intradermal skin testing (IST), as a lead-in to a series of subcutaneous provocation dose challenges, constitute the minimum requisites for diagnosis and management [4,5,13]. However, delayed-type hypersensitivity immune responses have also been shown to play a role in certain ALARs that occurred following oral or cutaneous anaesthesia. Consistently, in addition to the well-documented allergic contact dermatitis by topically applied LAs [1,2,14], positive patch tests (PT) and T cell involvement have also been observed in subjects experiencing contact dermatitis [3,5,15–17] or other adverse reactions [17–19] to LA injections. Furthermore, delayed local or systemic reactions have been reported in association with delayed positive IST results with LAs in many patients [4,5], some of whom were indeed shown later on to display delayed-type hypersensitivity to these drugs by *in vivo* specific PT [5,18,19] or *in vitro* specific T cell responses [17]. For these reasons, it has been proposed to perform IST with different, multiple concentrations and to evaluate possible delayed reactions after 24 h or more before patients can be permitted to undergo subcutaneous challenge [4,5]. Nevertheless, because of the high frequency of false positive IST results [4], other authors have proposed excluding this type of cutaneous test from the standard diagnostic procedure for assessment of LA sensitization [20,21].

Another related, unanswered issue, is that no exhaustive reports can be found in the literature as of yet with regard to the potential of LAs administered via skin/oral submucosal routes to induce immediate- and/or delayed-type hypersensitivity immune responses that may be predictive of adverse reactions to subsequent LA exposure. In fact, assessment of long-term persistence of LA non-reactivity has been carried out only in a few subjects and on the basis of indirect

clinical questionnaires with no objective diagnostic procedures challenging the actual, individual biological reactivity to these drugs [21]. Besides, it would be useful to determine a defined period of LA non-reactivity in order to reduce the number of unnecessary allergy consultations for these subjects.

One of the most used LAs in dental practice is mepivacaine, now available in whole glass vials without latex, which is present as a hidden allergen in dentists' gloves, dams and in glass tube vials for automatic injecting, and without preservatives and/or epinephrine, that are in part responsible for some ALARs [21–25]. The main aims of this study were therefore: (i) to define the clinical profiles of subjects admitted to the Allergy Section of our Department for specific concerns about amide LA use according to whether or not they had experienced previous adverse reactions to LAs or other drugs; (ii) to verify sensitization to mepivacaine and the duration of non-reactivity during post-testing appropriate clinical use of this amide LA in these subjects; and (iii) to assess the usefulness of a diagnostic protocol excluding IST but including PT for prediction of delayed type reactions to this amide LA. An accessory aim was to investigate the role of diagnostic 'confounders' such as latex, preservatives, vasoconstrictors and other chemicals, which are frequently either contaminants (latex) or necessary additives (preservatives, vasoconstrictors and other chemicals) in vials containing local anaesthetics.

Patients and methods

From October 1996 to September 1997, 247 consecutive patients, who shared concerns with their dentist/physician as to the safety of imminent administration of LAs, were referred to the outpatient Allergy Section of our Department. These subjects represented 8.5% of all patients ($n = 2905$) attending the allergy section during the same period. However, only 189 out of these 247 subjects were investigated for the first time for LA use-related concerns, representing 6.5% (189/2905) of all patients. To all these subjects, a prospective investigative trial, previously approved by the Department Ethical Committee, was proposed.

Diagnostic schedule to assess clinical profiles of patients and mepivacaine non-reactivity

A standard questionnaire, regarding family and personal history of systemic, respiratory, cutaneous and gastrointestinal complaints (i.e. oral itching, abdominal cramps, bloating, diarrhoea, gas, nausea, pyrosis, regurgitation, vomiting) suggestive of LA/drug-induced adverse reactions

or common atopic diseases, was initially given to each patient to define the reasons for allergy consultation.

Following this assessment, patients underwent SPT with 22 allergen extracts (all from Lofarma Labs, Milan, Italy) including local pollens (grasses mix, *Parietaria*, olive, hazel, mugwort, birch), inhalant (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat and dog dander, *alternaria*) and food allergens (wheat, rice, milk, egg, cod, beef, legume mix, tomato, potato, apple, orange), plus a latex extract (Lofarma Labs), a 2% mepivacaine solution free of latex, epinephrine, and preservatives (Astra Farmaceutici Italia, Milan, Italy), and a 2% preparation of the LA that was suspected to have possibly induced the ALAR, which was also epinephrine-, latex- and preservative-free. Moreover, SPT with appropriate concentrations of parahydroxybenzoic acid ester (1%) and sodium metabisulfite (5%) solution, as assessed by our previous experience (unpublished data), were performed. The results of SPT were recorded after 15 min and compared with HCl-histamine (10 mg/mL) as the standard positive reference and the diluent alone as negative control. SPT were considered to be positive when causing a weal with a mean diameter (the mean of the longest and the midpoint orthogonal diameters) at least 3 mm larger than the negative [26,27]. Any subject with at least one positive SPT result vs. the 22 common allergens used was considered atopic regardless of the presence of clinical symptoms/signs.

In order to assess the existence of specific delayed-type hypersensitivity immune responses and to prospectively evaluate the sensitizing potential of mepivacaine as opposed to that of classic haptens (parabens, Thiuram) and of a classic allergen (latex), PT was performed in all subjects using a 1% mepivacaine solution free of latex, epinephrine and preservatives, the same latex preparation used for SPT, a 16% parabens mixture emulsion in vaseline, a 1% Thiuram mix preparation in vaseline and a 0.1% isopropyl-paraphenylenediamine preparation in vaseline (Lofarma Labs). Patch tests were applied onto the healthy skin on the back using the Scanpor tape, removed after 48 h to allow development of the dermatitis-eczema local reaction, and read within 1–2 h [28]. All subjects with a negative PT reaction after 48 h were inspected again at 72 and 96 h before being definitively regarded as negative. The cell-mediated skin reaction was evaluated following the International Contact Dermatitis Research Group criteria [29] and graded according to the following score: 0 = negative or doubtful reaction (faint erythema only); 1 = weak positive reaction (erythema, infiltration, possibly papules); 2 = strong positive reaction (erythema, infiltration, papules, vesicles); 3 = extreme positive reaction (intense erythema, infiltration, and coalescing vesicles).

Subjects with both negative mepivacaine SPT and PT

were admitted to an integrated intradermal/subcutaneous mepivacaine challenge procedure with latex-free syringes (Becton Dickinson, Franklin Lakes, NJ, USA) in the course of a 1-day hospitalization.

Briefly, increasing doses of a 2% mepivacaine solution (0.02, 0.05, 0.1, 0.2, 0.5, 1.0 and 2.0 mL) were injected (by intradermal route the first two doses, by subcutaneous route the subsequent ones) on the extensor site of each patient's upper arm at 30-min intervals. An infusion line was set up at the beginning of the challenge and maintained for 30 min after the last injected dose.

Subjects with negative SPT but a positive PT with mepivacaine were admitted to the first mepivacaine intradermal dose (0.02 mL) but completed challenge only after an uneventful 24-h observation period.

Subjects with positive mepivacaine SPT result, if any, were considered allergic to mepivacaine and therefore excluded from this specific challenge and subjected to a diagnostic protocol for assessment of non-reactivity to a LA different from mepivacaine.

Subjects with negative challenge outcomes were considered non-reactive to mepivacaine and were permitted medical-approved use of this LA without latex, epinephrine and preservative and by a latex-free syringe. In addition, each patient was followed up every 6 months for the following 3 years. At each follow-up visit, the number of mepivacaine treatments experienced and the ALARs that possibly occurred were recorded. Furthermore, the prospective persistence of mepivacaine clinical non-reactivity was confirmed by a sequence of negative SPT, PT and by an uneventful challenge with increasing doses (0.05 mL by intradermal route, 0.5 mL and 1.5 mL by subcutaneous route) injected at 60-min intervals.

Statistical analysis

For categorical variables the chi-square test or exact test was performed as appropriate using the SPSS software package (release 10.0.5–1999, SPSS Inc., Chicago, IL, USA). Data are presented as means $\pm$ standard deviation. Probability values of 5% or less were considered as statistically significant.

Results

Patients and their retrospective clinical profiles

A total of 198 patients (80% response rate; 101 male, 97 female) gave their informed consent and entered the study. Ages varied from 8 to 66 years (27.9 ± 12.42). Only 72 subjects (36.4%) had previous ALARs (group 1). The remaining 126 subjects (63.6%) experienced previous adverse reactions to drugs other than LAs ($n = 71$; group

2), or reported only a previous alarming personal and/or familiar history of allergic-like complaints ($n = 55$; group 3).

Clinical picture of LA/other drug-induced adverse reactions and results of skin prick tests, patch tests and intradermal-subcutaneous challenges

The atopic condition, recurrent complaints, clinical picture and time course of ALARs, the LA suspected as causative agent and the results of the diagnostic trial in group 1 subjects are summarized in Table 1. In all previous ALAR cases (60 during a dental procedure and 12 during local cutaneous anaesthesia), the inducing LA was administered in an epinephrine-combined preparation, which was contaminated with latex (from the cap of the glass tube vial) and contained preservatives in most cases. Moreover, the instrumental manipulations (syringes, gloves) could not be considered completely latex-free in most of the examined cases.

Forty-eight subjects (76.3%) reported ALARs with objective signs such as flush, local oedema/erythema, urticaria, dyspnoea/persistent wheeze and sudden loss of consciousness. In the same group, 24 subjects had subjective complaints; commonly, shakiness, near fainting and nausea, but also migraine, paresthesia and shortness of breath. In 25 cases in the 'objective' ALAR subgroup, signs arose immediately and included also six cases of sudden loss of consciousness. A point worth noting is that 31 of the patients with objective signs, including the subjects with loss of consciousness, and all the subjects with subjective complaints did not receive any treatment at the time of the reaction because of rapid, spontaneous vanishing of symptoms. On the contrary, seven previously defined asthmatic subjects who suffered from intermediate/delayed persistent wheezing following LA injection, nine subjects all having immediate and persistent diffuse urticaria with local oedema, and one subject with delayed diffuse flush, migraine and delayed, local itching erythema with inflammatory oedema, were treated with β_2 -agonists and steroids, and antihistamines plus steroids, respectively. In this group, 11 subjects had a positive latex SPT. Of note, the nine subjects with immediate persistent urticaria/oedema included eight atopic subjects, had a constant previous history of recurrent acute urticaria and/or gastrointestinal symptoms, and displayed positive latex SPT, as is often the case in subjects with latex allergy because of cross-sensitivity to many food allergens. On the other hand, the subject with delayed diffuse flush, migraine and local oedema had a positive mepivacaine PT.

In this group, 71 patients who had negative skin responses to both SPT and PT with mepivacaine, including all subjects with positive latex SPT, completed mepiva-

caine challenge with uneventful outcomes. On the contrary, the patient with the isolated positive mepivacaine PT developed local intense erythema, oedema and itching 24 h after the first (0.02 mL) intradermal mepivacaine challenge. Thereafter, the challenge was discontinued and signs of ALAR were promptly and efficiently cured with antihistamines and local steroids. No subject in this group had a positive SPT with mepivacaine or other inducing LA free of latex, preservative and epinephrine (Table 1).

The results of the diagnostic trial and mepivacaine challenge in group 2 and group 3 subjects are summarized in Tables 2 and 3, respectively.

In group 2, almost half of the subjects (33/71; 46.5%) were also suffering from recurrent, similar allergic complaints, but only 21, including the patients of the subgroup with a positive latex SPT, were really atopic, as shown by positive SPT results to common allergens. In this group, 18 patients reported symptoms of adverse drug-induced reactions that were similar to the previously and spontaneously recurrent ones. Finally, all patients had negative results by mepivacaine diagnostic and challenge procedures (Table 2).

With regard to group 3 subjects, the most striking feature was that 44 out of the 55 subjects (80.0%) were atopic. Ten non-symptomatic subjects, of whom three were also atopic, were young subjects and had a family history of atopic diseases that also included previous adverse drug-induced reactions in six cases. Latex SPT were positive in two subjects, whereas mepivacaine diagnostic and challenge procedures were positive only in one atopic subject who displayed a positive mepivacaine PT and local delayed oedema after the first (0.02 mL) intradermal mepivacaine challenge (Table 3).

More than half (105/198 subjects; 53%) of the entire examined cohort consisted of atopic subjects as defined by SPT results with common allergens. The inter-groups distribution of atopic subjects was significantly lower ($P < 0.001$) in the group with previous adverse drug-induced reactions (21/71) than in the other two groups (group 1 = 40/72; group 3 = 44/55). A few subjects had a positive SPT to latex (15/198; 7.6%), parahydroxybenzoic acid ester (4/198; 2.1%) or a positive parabens PT (6/198; 3%), with group 1 subjects having a significantly higher frequency either for latex SPT ($P = 0.008$) or for parabens PT ($P = 0.04$) than the other two groups.

None of the subjects had a positive SPT with the 5% metabisulfite solution (data not shown).

Follow-up results

Of the 196 subjects who were followed-up, only 187 completed the scheduled trial, as six subjects in group 2 and three subjects in group 3 refused to continue the trial even

Table 1. Results of the diagnostic protocol and mepivacaine challenge in subjects with a previous history of adverse local anaesthetic reactions

Subjects (<i>n</i> = 72)	Number of subjects with positive family history of atopy	Adverse local anaesthetic-induced reaction			Recurrent complaints in atopic/non-atopic subjects (number with complaints)				Number of subjects with positive skin tests										Response to challenge with MEP		
					Atopic <i>n</i> = 40		Non-atopic <i>n</i> = 32		MEP		OLA		L		PA		THI			IPPHE	
		Clinical picture	Time- course	Inducers	Tot.	Tot.	S	P	S	P	S	P	S	P	S	P	S	P			
1–3	3	U/LO	IMM	ART/EPI	U (2), A (1), R (2)	2	U (1), GS (1)	1	–	–	–	–	3	–	1	1	nd	1	nd	–	–
4–7	2	U/LO	IMM	MEP/EPI	U (3), R (3), A (2)	4	–	–	–	–	nd	nd	4	1	–	–	nd	1	nd	–	–
8–9	2	U/LO	IMM	LID/EPI	GS (2), U (2), R (2)	2	–	–	–	–	–	–	2	–	–	1	nd	–	nd	–	–
10–13	2	SLC	IMM	LID/EPI	GS (2)	2	GS (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
14–15	1	SLC	IMM	ART/EPI	R (1)	1	GS (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
16–21	–	F	IMM	MEP/EPI	–	–	–	–	–	–	nd	nd	–	–	–	–	nd	–	nd	–	–
22	–	F	IMM	ART/EPI	U (1), GS (1)	1	–	–	–	–	–	–	–	–	–	–	nd	–	nd	–	–
23	–	DY/VO	IMM	ART/EPI	R (1), GS (1)	1	–	–	–	–	–	–	–	–	–	–	nd	–	nd	–	–
24–25	1	F	IMM	LID/EPI	–	–	–	–	–	–	–	–	–	1	–	nd	–	nd	–	–	–
26–28	–	SHA/NF	IMM	MEP/EPI	R (3), A (1)	3	–	–	–	–	nd	nd	–	–	–	–	nd	–	nd	–	–
29–30	–	SHA/PAR	IMM	MEP/EPI	U (1), GS (1)	1	GS (1)	1	–	–	nd	nd	–	–	–	–	nd	–	nd	–	–
31–33	–	MIG/NF	IMM	MEP/EPI	R (3), GS (2)	3	–	–	–	–	nd	nd	–	–	–	1	nd	–	nd	–	–
34–38	2	SHA/SB	IMM	LID/EPI	R (4), U (2)	5	–	–	–	–	–	–	–	1	–	nd	–	nd	–	–	–
39–43	2	SHA/PAR	IMM	LID/EPI	U (1), GS (2)	2	GS (2), U (1)	3	–	–	–	–	–	–	–	–	nd	–	nd	–	–
44–48	1	SHA/NF	IMM	ART/EPI	R (3), A (2)	4	GS (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
49	–	SB/SHA	IMM	ART/EPI	–	–	GS (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
50–52	2	PW	INT	LID/EPI	A (3)	3	–	–	–	–	–	–	–	–	–	–	nd	–	nd	–	–
53	1	PW	INT	MEP/EPI	A (1)	1	–	–	–	–	nd	nd	–	–	–	–	nd	–	nd	–	–
54–55	2	PW	DEL	MEP/EPI	A (2)	2	–	–	–	–	nd	nd	–	–	–	–	nd	–	nd	–	–
56	1	PW	DEL	LID/EPI	A (1)	1	–	–	–	–	–	–	1	–	–	–	nd	–	nd	1	–
57	1	LO/LER/F/MIG	DEL	MEP/EPI	–	–	–	–	–	1	nd	nd	–	–	–	–	nd	1	nd	–	1
58–63	1	F	INT	MEP/EPI	–	–	U (3)	3	–	–	nd	nd	1	–	–	–	nd	–	nd	–	–
64–69	1	F	INT	LID/EPI	–	–	–	–	–	–	–	–	–	–	1	nd	–	nd	–	–	–
70–72	–	F	INT	ART/EPI	–	–	–	–	–	–	–	–	–	–	1	nd	–	nd	–	–	–
Total	25					38		12	0	1	0	0	11	1	3	5	–	3	–	1	1

MEP: Mepivacaine; OLA: Other local anaesthetic; L: Latex; PA: Parabens; THI: Thiuram mix; IPPHE: Isopropyl-paraphenylenediamine; S: Skin prick test; P: Patch test; U: Urticaria; LO: Local oedema; SLC: Sudden loss of consciousness; F: Flush; DY: Dyspnoea; VO: Vomit; SHA: Shakiness; PAR: Paresthesia; MIG: Migraine; NF: Near fainting; SB: Shortness of breath; PW: Persistent wheeze; LER: Local erythema; IMM: Immediate (< 30 min); INT: Intermediate (30–120 min); DEL: Delayed (> 120 min); ART: Articaine; EPI: Epinephrine; LID: Lidocaine; R: Rhinitis; A: Asthma; GS: Gastrointestinal symptoms; nd: not done; Tot.: total.

Table 2. Results of the diagnostic protocol and mepivacaine challenge in subjects with a previous history of adverse drug-induced reactions

Subjects (<i>n</i> = 71) Females = 35	Number of subjects with positive family history of atopy	Adverse drug anaesthetic-induced reaction		Recurrent complaints in atopic/non-atopic subjects (number with complaints)				Number of subjects with positive skin tests										Response to challenge with MEP
				Atopic (<i>n</i> = 21)		Non-atopic (<i>n</i> = 50)		MEP		L		PA		THI		IPPHE		
		Clinical picture	Inducers	Tot.		Tot.		S	P	S	P	S	P	S	P	S	P	
1–14	4	U	NSAIDs	U (1)	1	U (4)	4	–	–	–	–	–	–	nd	–	nd	–	–
15–32	5	U	β-LAC	U (1), GS (2)	3	U (4)	4	–	–	1	–	–	–	nd	1	nd	–	–
33–41	3	U	NSAIDs/β-LAC	U (1), GS (1)	2	U (2), GS (1)	3	–	–	1	–	–	–	nd	–	nd	1	–
42	1	U	SULPH	R (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
43–49	–	MIG	NSAIDs	–	–	MIG (3), GS (2)	5	–	–	–	–	–	–	nd	–	nd	–	–
50–53	1	MIG	β-LAC	R (1)	1	GS (2)	2	–	–	–	–	–	–	nd	–	nd	–	–
54	–	MIG	SULPH	–	–	–	–	–	–	–	–	–	–	nd	–	nd	–	–
55–58	1	NF	NSAIDS	R (1)	1	GS (3)	3	–	–	–	–	–	–	nd	–	nd	–	–
59–63	2	NF	β-LAC	–	–	GS (1)	1	–	–	–	–	–	–	nd	–	nd	–	–
64–65	–	NF	NSAIDs/β-LAC	–	–	–	–	–	–	–	–	–	–	nd	–	nd	–	–
66	–	STJ	NSAIDs	–	–	–	–	–	–	–	–	–	–	nd	–	nd	–	–
67	1	STJ	MTZ	R (1), A (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
68–70	2	A	NSAIDs	A (1)	1	A (2)	2	–	–	–	–	–	–	nd	–	nd	–	–
71	–	A	NSAIDs/β-LAC	A (1)	1	–	–	–	–	–	–	–	–	nd	–	nd	–	–
Total	20				12		24	0	0	2	0	0	0	–	1	–	1	0

MEP: Mepivacaine; L: Latex; PA: Parabens; THI: Thiuram mix; IPPHE: Isopropyl-paraphenylenediamine; S: Skin prick test; P: Patch test; U: Urticaria; MIG: Migrain; NF: Near fainting; STJ: Steven Johnson syndrome; A: Asthma; NSAIDs: Non steroid anti-inflammatory drugs; β-LAC: β-Lactam antibiotics; SULPH: Sulphonamides; MTZ: Metimazole; R: Rhinitis; GS: Gastrointestinal symptoms; nd: not done; Tot.: Total.

Table 3. Results of the diagnostic protocol and mepivacaine challenge in subjects with a previous personal or family history of allergy-like symptoms

Subjects (<i>n</i> = 55) Females = 29	Number of subjects with positive family history of atopy	Recurrent complaints in atopic/non-atopic subjects (number with complaints)				Number of subjects with positive skin tests								Response to challenge with MEP		
		Atopic (<i>n</i> = 44)		Non-atopic (<i>n</i> = 11)		MEP		L		PA		THI			IPPHE	
		Tot.		Tot.		S	P	S	P	S	P	S	P		S	P
1–10	10	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
11–18	5	R (8)	8	–	–	–	–	–	–	–	–	–	–	–	–	–
19–36	15	R (17), A (17)	17	R (1), A (1)	1	–	–	–	–	–	–	–	–	–	–	–
37–39	2	GS (3)	3	–	–	–	–	–	–	–	–	–	–	–	–	–
40	1	GS (1)	1	–	–	–	–	1	–	–	–	–	–	–	–	–
41–42	1	–	–	ACD (2)	2	–	–	–	–	–	–	–	–	–	–	–
43	1	ACD (1)	1	–	–	–	1	–	–	–	1	–	1	–	–	1
44–52	5	U (8)	8	U (1)	1	–	–	–	–	–	–	–	–	–	–	–
53	1	U (1)	1	–	–	–	–	1	–	1	–	–	–	–	–	–
54–55	1	U (2), O (2)	2	–	–	–	–	–	–	–	–	–	–	–	–	–
Total	42		41		4	0	1	2	0	1	1	0	1	0	0	1

MEP: Mepivacaine; L: Latex; PA: Parabens; THI: Thiuram mix; IPPHE: Isopropyl-paraphenylenediamine; S: Skin prick test; P: Patch test; R: Rhinitis; A: Asthma; GS: Gastrointestinal symptoms; ACD: allergic contact dermatitis; U: urticaria; O: oedema; Tot.: Total.

though they had tolerated mepivacaine challenges and uneventful local anaesthetics during the first semester of survey. During follow-up, a total of 1017 mepivacaine treatments were administered (mean 5.4/each, range 1–46, Fig. 1) and all were uneventful. Almost all of the investigated subjects (174/187; 93%) had more than one mepivacaine treatment during follow-up, which in most cases was administered during the first semester (169/187; 90.4%) following controlled challenge.

Finally, in each diagnostic session for control of sensitization/reactivity to contaminant/additive-free mepivacaine, positive results with mepivacaine SPT and/or PT or challenge were never observed.

Discussion

The present study shows that more than 60% of patients in our series who were referred for allergy work-up did not have a specific history of previous ALARs. Moreover, no reactions to treatment with contaminant/additive-free mepivacaine under controlled conditions were observed in all the subjects who completed the scheduled 3-year follow-up. In fact, persistent absence of sensitization and clinical reactivity to mepivacaine, in the absence of contaminants (i.e. latex), and preservatives and vasoconstrictors, lasted for at least 3 years during clinical use, and it was independent of the number and frequency of drug treatments as it was shown to be stable for both the lower (1) and the higher (46) number of re-administrations as well

as for both the lower (0.02) and the higher (1.3) monthly means of treatments reported during follow-up. The data presented here on mepivacaine clinical non-reactivity persistence are consistent with the only study reported in the literature [21], but are derived from a larger number of subjects and are further strengthened by the periodical drug controlled challenge and by the assessment of objective parameters of biological sensitization such as skin prick testing and patch testing. Moreover, it must not be overlooked that these data are also more homogeneous, as they are derived from subjects treated and challenged only with mepivacaine.

With regard to the diagnostic session, none of the 198 investigated patients showed a positive SPT response to contaminant/additive-free LA solutions, including the 49 patients reporting previous specific LA-induced subjective or objective immediate complaints. Furthermore, and of major interest, after preliminary diagnostic assessment by specific SPT and PT, mepivacaine challenge was completely uneventful in all subjects displaying negative skin-specific responses to both tests.

Our data indicate that true allergic ALARs, as reactions induced by specific IgE vs. LA molecules, did not occur in group 1 patients, and, consistently with some old [20,30–34] and more recent [5] literature reports, confirm that, at least among amide-type LAs, such reactions are extremely rare.

Moreover, the data regarding the eventful outcomes of the challenge observed in both patients previously displaying positive PT demonstrate that PT is reliable for the

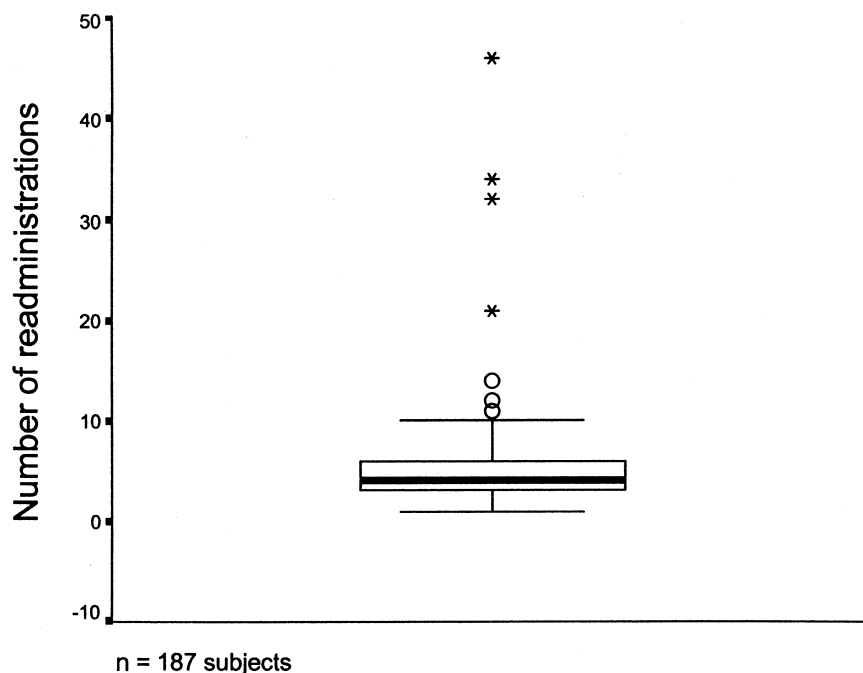


Fig. 1. Distribution and dispersion of the total number of re-administrations in the 187 subjects who completed the study. Box plot represents: median (thick line), 25–75% (box), 10–90% (thin line), outliers (O), extremes (*).

prediction of delayed type reactions to amide LAs that reportedly account for a substantial part of unexpected ALARs [4,5,18,19]. Clearly, if amide LA PT is confirmed in larger studies to be able to predict positive subcutaneous challenge tests, these latter could also be possibly omitted. It also should not be overlooked that, in the case of a pre-existing delayed-type allergy to amide LAs, with or without a history of previous ALAR, PT is unlikely to induce systemic delayed reactions (although it may induce severe local eczema), as is sometimes the case after IST [4,5]. Therefore, amide LA PT, as a reliable and safe diagnostic tool for amide LA reactivity assessment, should be considered for future investigations of subjects with demonstrated amide LA negative SPT with or without a clear history of previous ALAR.

Finally, this study confirms that assessment of patients with alleged history of ALARs is difficult and that a precise classification of the referred complaints is not completely definite. Nevertheless, the high frequency of immediate allergic reactions to latex and delayed cutaneous sensitivity to parabens found among patients with previous ALARs suggests that at least some of the reported ALARs may be immune-mediated and probably provoked by these hidden allergens rather than by the more accredited non-immune toxic/psychomotor responses and vasovagal reactions [4,35] or by LA/operative trauma-induced direct histamine release [5]. In this regard, because common allergen positive SPT is a prominent risk factor for developing sensitization vs. latex or other occupational allergens [36,37], it is noteworthy that among subjects with previous

ALARs there was a frequency of atopy that was similar to that present among subjects with only alleged recurrent allergic-like complaints and significantly higher than that present among subjects with alleged previous adverse reactions to drugs other than LAs.

In conclusion, the present study indicates once more that true allergy to LAs is exceptional. Our diagnostic protocol for ALARs is not less time consuming than those previously proposed [4,5]; however, in our experience, it was shown to be more reliable and, above all, safer. In fact, because our data show that PT screening can predict delayed-type reactions, the proposed diagnostic protocol represents an improvement to ALAR diagnosis, since only immediate-type reactions, when associated to false negative SPT, remain unpredictable at present. Finally, follow-up data indicate that during the 3 years following a demonstrated absence of sensitization and clinical reactivity to mepivacaine, it is entirely unnecessary to subject patients to both the trauma and expense of SPT and controlled challenge to assess sensitization and reactivity modifications, respectively. Contaminant-free mepivacaine may safely be given to such patients. Despite these considerations, over the last few years, the percentage of subjects among all patients attending our Allergy Section referred for LA reactivity assessment has increased from 4.5% in 1992–93 to 8.5% in 1996–97, of which the percentage of 'new patients' examined for the first time for LA reactivity assessment during the same time periods was 4% and 6.5%, respectively. Thus, the percentage of patients referred for repeat amide LA reactivity assessment has

increased from 11.1% to 23.5%. Moreover, the percentage of subjects referred for allergy evaluation because of dentist/physician concerns due to pre-existing adverse reactions induced by drugs other than LA, or owing to simple atopic disease, has increased from 29.4% in 1992–93 to 63.6% in 1996–97. Therefore, specific programmes of continued medical education regarding ALARs, and further investigative trials to design low-cost, safe and accurate diagnostic protocols, as well as to assess the most protracted persistence of non-reactivity to amide LAs, are needed in order to prevent this problem of allergy work-up overload on national public health services.

References

- Lane CG, Luikart R. Dermatitis from local anesthetics. *JAMA* 1951; 146:717–20.
- Curley RK, Macfarlane AW, King CM. Contact sensitivity to the amide anesthetics lidocaine, prilocaine and mepivacaine. *Arch Dermatol* 1986; 122:924–6.
- Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. *Contact Dermatitis* 1991; 25:45–8.
- Schatz M. Skin testing and incremental challenge in the evaluation of adverse reactions to local anesthetics. *J Allergy Clin Immunol* 1984; 74:606–16.
- Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996; 97:933–7.
- McCaughy W. Adverse effects to local anesthetics. *Drug Safety* 1992; 7:178–9.
- Cawson RA, Curson I, Whittington DR. The hazards of dental local anesthetics. *Br Dent J* 1983; 154:253–8.
- Huwyler T, Bon A, Wüthrich B. Allergische und pseudallergische Reaktionen in Zusammenhang mit zahnärztlichen Eingriffen. *Schweiz Monatsschr Zahnmed* 1990; 100:751–5.
- Milgrom P, Fiset L. Local anaesthetic adverse effects and other emergency problems in general dental practice. *Int Dent J* 1986; 36:71–6.
- Dukor P, Kallos P, Schlumberger HD, West GB. *PAR (Pseudo-Allergic Reactions)*. Basel: Karger, 1980.
- Bonnet MC, du Cailar G, Deschodt J. Anaphylaxis caused by lidocaine. *Ann Fr Anesth Reanim* 1989; 8:127–9.
- Bourezane Y, Adessi B, Didier JM, Vuitton DA, Laurent R. Allergie immédiate aux anesthésiques du groupe amide. *Gastroenterol Clin Biol* 1997; 21:344–5.
- Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. *Ann Pharmacother* 1996; 30:851–7.
- Ruzicka T, Gerstmeier M, Przybilla B, Ring J. Allergy to local anesthetics: comparison of patch test with prick and intradermal results. *J Am Acad Dermatol* 1987; 16:1202–8.
- Suhonen R, Kanerva L. Contact allergy and cross-reactions caused by prilocaine. *Am J Contact Dermat* 1997; 8:231–5.
- Bircher AJ, Messmer SL, Surber C, Ruffli T. Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; 34:387–9.
- Zanni MP, Mauri-Hellweg D, Brander C et al. Characterization lidocaine-specific T cells. *J Immunol* 1997; 158:1139–48.
- Adler P, Simon M. Contribution to the problem of allergy to local anesthetics. *Oral Surg* 1949; 2:1029–36.
- Aldrete JA, O'Higgins JW. Evaluation of patients with history of allergy to local anesthetic drugs. *South Med J* 1971; 64:1118–21.
- Chandler MJ, Grammer LC, Patterson R. Provocative challenge with local anesthetics in patients with a prior history of reactions. *J Allergy Clin Immunol* 1987; 79:883–6.
- Wasserfallen JB, Frei PC. Long-term evaluation of usefulness of skin and incremental challenge tests in patients with history of adverse reaction to local anesthetics. *Allergy* 1995; 50:161–5.
- Schwartz HJ, Sher TH. Bisulfite sensitivity manifesting as allergy to local dental anesthesia. *J Allergy Clin Immunol* 1985; 75:525–7.
- Doom-Goossens A, De Alam AG, Degreef H, Kochuyt A. Local anaesthetic intolerance due to metabisulfite. *Contact Dermatitis* 1989; 20:124–6.
- Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984; 74:623–30.
- Axelsson JG, Johansson SGO, Wrangsjö K. IgE-mediated anaphylactoid reactions to rubber. *Allergy* 1987; 42:46–50.
- Bernstein L. Proceedings of the task force on guidelines for standardizing old and new technologies used for the diagnosis and treatment of allergic diseases. *J Allergy Clin Immunol* 1988; 82:487–526.
- Astarita C, Franzese A, Scala G, Sproviero S, Raucchi G. Farm workers' occupational allergy to *Tetranychus urticae*: clinical and immunological aspects. *Allergy* 1994; 49:466–71.
- Wilkinson JD, Shaw S. Contact Dermatitis. In: Kay AB, ed. *Allergy and Allergic Disease, Volume II*. Oxford: Blackwell Science, 1997:1608–31.
- Wilkinson DS, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Dermatol Venereol* 1970; 50:287–92.
- de Shazo RD, Nelson HS. An approach to the patient with a history of local anaesthetic hypersensitivity experience with 90 patients. *J Allergy Clin Immunol* 1979; 63:387–94.
- Le Sellin J, Drouet M, Bonneau JC, Sabbah A. Conduite à tenir dans les suspicions d'allergie à la lidocaine. *Allergie Immunologie* 1986; 18:35–8.
- Escolano F, Aliaga L, Álvarez J, Alcon A, Olivé A. Reacciones alérgicas a los anestésicos locales. *Rev Esp Anestesiol Rianim* 1990; 37:172–5.
- Fisher M, Graham R. Adverse responses to local anesthetics. *Anaesth Intensive Care* 1984; 12:325–7.
- Incaudo G, Schatz M, Patterson R et al. Administration of local anesthetics to patients with a history of prior adverse reactions. *J Allergy Clin Immunol* 1978; 61:339–45.
- De Jong RH. Toxic effect of local anaesthetics. *JAMA* 1978; 239:1166–8.
- Bernstein IL, Bernstein DI. Occupational asthma. In: Middleton E, Reed CE, Ellis EF et al. eds. *Allergy: principles and practice*. 5th edn. St Louis: Mosby, 1999: (Vol. II) 963–80.
- Liss GM, Sussman GL, Deal K et al. Latex allergy: epidemiological study of 1351 hospital workers. *Occup Environ Med* 1997; 54:335–42.