

T-cell reaction to local anaesthetics: relationship to angioedema and urticaria after subcutaneous application — patch testing and LTT in patients with adverse reaction to local anaesthetics

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Summary

Background Local anaesthetics are known to elicit T-cell reactions after epicutaneous application, namely contact dermatitis. In addition, adverse reactions like urticaria and angioedema are rather common after submucosal or subcutaneous injection. The pathogenesis of these side-effects, which appear frequently hours after application, is unknown, but thought to be not immunoglobulin E-mediated, since immediate skin tests are mostly negative.

Objectives We investigated whether patients who developed urticaria and angioedema after subcutaneous application have a T-cell sensitization to local anaesthetics, which might be responsible for the symptoms.

Methods Twenty patients with generalized and/or local cutaneous reactions after LA were examined with intradermal testing using a standard panel of six LAs and patch testing using between seven and nine LAs in vaseline and four LAs in PBS. In 10 patients, a lymphocyte transformation test (LTT) was performed.

Results Only 2/20 patients had an immediate skin reaction (positive intradermal test), whereas 6/20 patients had a positive delayed skin reaction (positive patch test). In 6/10 subjects the LTT was positive.

Conclusions Delayed appearance of urticaria and angioedema after subcutaneous application of local anaesthetics may be related to a T cell-mediated sensitization, which might be detected by patch testing or LTT.

Keywords: adverse reactions, angioedema, local anaesthetics, lymphocyte transformation test, patch testing, T cell-mediated reaction, urticaria

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Introduction

Local anaesthetics (LAs) are frequently used drugs that allow surgical or dental procedures to be performed safely and comfortably without the risks of general anaesthesia. Moreover, the anti-arrhythmic activity of some of these drugs can be uniquely life-saving. Although often considered as intrinsically safer than general anaesthesia, LAs can

elicit a variety of adverse reactions (AR) [1]. Many patients and some clinicians declare any untoward reaction after injection of LA as an allergy, but in reality, true allergic reactions to LA are thought to be rare. In several studies, allergic side-effects were estimated to account for about 1% of all reported AR [2,3].

Various mechanisms have been proposed to explain AR after LA. Most of these reactions such as vasovagal collapse, nausea or dyspnea are believed to be of psychogenic or pharmacological origin [3–7]. However, such

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mechanisms can hardly explain symptoms such as urticaria and angioedema.

Drug allergies are usually classified according to the hypersensitivity reactions type I to IV defined by Gell and Coombs [8]. LAs are known to be responsible for a T cell-mediated delayed-type allergy (= type IV hypersensitivity reaction) with its typical manifestation as a contact dermatitis after topical application [5,6,9–11].

Quite a few patients develop urticaria or angioedema after subcutaneously applied LA [1]. In general, these symptoms are not associated with a T cell-mediated reaction. They are considered to be IgE- or complement-mediated or pseudoallergic, the latter implying a nonimmune-mediated degranulation of mast cells and/or basophils, since immediate intradermal skin tests with LA are almost consistently negative in these patients. However, it is unclear what type of clinical manifestation develops in patients suffering from contact dermatitis to epicutaneous application of LA, if the same drug is applied subcutaneously. With this in mind, we sought to investigate, whether T cell-mediated mechanisms may account for some, mainly delayed appearing skin symptoms like urticaria and angioedema observed in some patients after LA.

Patients and methods

Patients

Two per cent (128/5883) of subjects consulting our outpatient allergy clinic during a 2.6-year period had developed at least one episode of AR after LA. They were investigated in this study. Twenty-eight per cent (36/128) had developed urticaria and/or angioedema, or itching exanthema (five patients with angioedema and urticaria in anaphylactic shock were not included). Twenty of these patients agreed to the performance of patch testing with LAs. Six persons with previous contact to local anaesthetics but without history of adverse reactions to epicutaneous or subcutaneous application served as control group.

Skin testing

Intradermal testing was performed to demonstrate the presence of LA-specific immunoglobulin (Ig) E antibodies on skin mast cells. In all 20 subjects a standard panel of six commonly used LAs in concentrations of 0.005–0.5% was tested: lidocaine (Xylocain®), mepivacaine (Scandicain®), prilocaine (Xylonest®) and bupivacaine (Carbostesin®) (Astra Pharmaceutica AG, Dietikon, Switzerland); articaine (Ultracain®) (Hoechst AG, Frankfurt, Germany) and procaine (Syntocain®) (Sintetica SA, Mendrisio, Switzerland). One milligram per millilitre histamine diphosphate served

as positive, and 0.9% sodium chloride as negative control. To exclude skin reactions to preservatives present in some LA preparations, we also applied propylparahydroxybenzoate (0.2%), methylparahydroxybenzoate (1.3%) and sodium disulfite (1%), (Hänseler AG, Herisau, Switzerland). A commercially available latex extract (Stallergenes SA, Fresnes, France) was tested as well. The skin reaction (weal and flare) after 20 min to the applied substances was recorded as recommended by Schatz [12].

Patch testing was performed to show an *in vivo* T-cell sensitivity to LAs. In 17/20 patients, we used nine LAs (benzocaine 5%, procaine HCl 2%, tetracaine HCl 1%, lidocaine HCl 15%, cinchocaine HCl 5%, mepivacaine HCl 1%, articaine 1%, bupivacaine 1%, oxybuprocaine 1%) in vaseline (Theomed AG, Greifensee, Switzerland) and four LAs (lidocaine, oxybuprocaine, procaine, mepivacaine, each 5%) in PBS. In three patients, only seven LAs in vaseline were applied (without bupivacaine and oxybuprocaine). Whereas the concentrations of the commercial vaseline-based LAs range from 1 to 15%, LAs in PBS were always freshly prepared just before use in a concentration of 5%. Vaseline and PBS served as negative control. The patch test was performed using leukotest tape (Beiersdorf AG, Hamburg, Germany), which was left on the skin for 48 h. Patch tests were read at 48 and 72 h. Reactions were scored as recommended by the International Contact Dermatitis Research Group [13].

LTT (lymphocyte transformation test)

This test was performed to demonstrate an *in vitro* T-cell sensitivity to LAs [14]. In 10/20 patients with presumable allergy to LAs, peripheral blood mononuclear cells (PBMCs) were obtained after the drug allergy symptoms had subsided. Briefly, freshly isolated PBMCs ($1\text{--}2 \times 10^6$ cells in 1 mL culture media) from these patients were cultured in upright 12-mL tubes (Falcon 3033) in the presence of different drug concentrations. After 6 days, [^3H]thymidine (0.5 μCi) was added for 14 h, cultures were harvested, and c.p.m. were measured in a beta counter (Packard, Canberra Corporation, Meriden, CT, USA). Stimulation indices (SI) were calculated as c.p.m. in culture with antigen/c.p.m. in culture without antigen and considered positive if > 2 .

Results

Patients

Symptoms reported in 128 subjects who had experienced an AR to LAs are summarized in Table 1 (mean age 44.9 years (range 6–85 years); male:female, 2.5:1). Thirty-six of these patients (28%) had developed urticaria and/or

Table 1. Symptoms reported following injection of local anaesthetics (n = 128)

Symptom	n
<i>Skin (N = 108)</i>	
Urticaria only	8
Angioedema only	7
Urticaria & angioedema*	9
Itching exanthema only	13
Angioedema & itching exanthema	4
Paleness, blisters, erosive lesions	67
<i>Central nervous system (N = 68)</i>	
Nausea	21
Vertigo	15
Cramps (clony)	8
Paresthesia, headache, unconsciousness	24
<i>Cardiovascular system (N = 65)</i>	
Collapse	27*
Tachycardia	18
Drop of blood pressure	8
Increase of blood pressure, heart failure, palpitations	12
<i>Respiratory system (N = 42)</i>	
Dyspnea	20
Obstruction of the pharynx	7
Epistaxis, cough, hyperventilation	15
<i>Gastrointestinal tract (N = 17)</i>	
Dysphagia	6
Diarrhoea	3
Abdominal pain, emesis, indisposition	8

*Including five patients with anaphylactic shock

angioedema or itching exanthema. The characteristics of the skin symptoms in these patients are shown in Table 2. Interestingly, most skin symptoms after subcutaneous application of LA occurred delayed, namely >2 h after the application. LAs responsible for these reactions were mainly of the amide-type, as the ester-types are used infrequently.

Skin testing and LTT

Twenty of the 36 patients with skin symptoms participated in this study. In all subjects, intradermal skin tests and patch tests were performed to detect a possible sensitization to LAs. Ninety per cent of subjects (18/20) had negative intradermal tests to the standard panel of LA. Two of twenty patients (10%) had a positive intradermal test to prilocaine and mepivacaine or to lidocaine, articaine and procaine, respectively. Since the intradermal skin tests were almost consistently negative, we performed patch tests to demonstrate whether allergic skin reaction could have been

Table 2. Characteristics of skin symptoms in 36 patients

Characteristics	N
<i>Skin symptoms</i>	
Urticaria	12
Local	7
Generalized	5
Combined with angioedema	4
Angioedema	15
Local	14
Generalized	1
Combined with urticaria	4
Combined with itching exanthema	4
Itching exanthema	17
Local	10
Generalized	7
Combined with angioedema	4
<i>Onset of symptoms</i>	
Immediate (<2 h)	11
Delayed (>2 h)	25
<i>Application of LA</i>	
Epicutaneous*	4
Subcutaneous	30
Both†	2
<i>Suspected LA</i>	
Amide type	23
Ester type	2
Unknown	11

*Symptoms: itching exanthema (1), eczema (2), angioedema and itching exanthema (1). †Symptoms: itching exanthema (1), angioedema (1).

the manifestation of a T-cell sensitivity to LA rather than the consequence of an IgE-mediated immune response. Indeed, a higher percentage of patients reacted, as 6/20 patients (30%) had a positive patch test. However, only in 3/6 positive patch tests, did the reacting LA correlate exactly with the LA of the history.

To ascertain whether skin tests correlate with an *in vitro* test, we performed LTT in 10 subjects, including the six patch test-positive patients. Six of ten subjects (60%) had a positive LTT. Three of these six patients also had a positive patch test. In 5/6 patients with a positive LTT, the reacting LA correlated exactly with the LA of the history. In 1/6 patients (number 5) of the same subgroup, the reacting LA was possibly cross-reactive to the LA of the AR, since lidocaine and mepivacaine are cross-reactive in most patients (Table 3).

Table 3. Characteristics of nine patients with T-cell sensitivity to LA

Patient	LA of history	Skin symptoms†	Test (SI)	LA tested								No Ag (c.p.m.)
				L	M	B	A	C	P	O	T	
1	L	Eczema (top)	LTT	15.0*	9.2	0.2	nd	nd	0.7	0.7	1.1	596
		Local angioedema (sc)	Patch	+++	+	–	–	–	–	–	–	
2	L, M	Eczema (top)	LTT	14.1	13.6	nd	nd	nd	8.4	nd	nd	1682
		Local angioedema (sc)	Patch	++	–	nd	–	–	–	nd	–	
3	A, L	Local angioedema	LTT	58.1	nd	3.0	nd	nd	3.8	nd	nd	574
		Pruritus (sc)	Patch	–	–	–	–	–	–	–	–	
4	A	Generalized urticaria (sc)	LTT	1.2	1.6	nd	3.5	nd	nd	nd	nd	2094
			Patch	–	–	–	–	–	–	–	–	
5	M	Local urticaria (sc)	LTT	3.5	0.6	nd	nd	nd	nd	nd	nd	2130
			Patch	–	–	–	–	–	–	–	–	
6	A, L	Local angioedema (sc)	Patch	+	–	–	–	–	–	+	–	
7	A, L	Generalized itching	Patch	–	–	–	–	–	–	+	–	
		Exanthema (sc)										
8	A, B, P	Local angioedema (sc)	Patch	+	–	–	–	+	–	–	–	
9	Amide-LA**	Generalized urticaria (sc)	LTT	3.9	nd	nd	2.0	nd	nd	nd	nd	628
			Patch	–	–	nd	–	–	+	nd	–	

L = lidocaine, M = mepivacaine, B = bupivacaine, A = articaine, P = prilocaine, C = cinchocaine, P = procaine, O = oxybuprocaine, T = tetracaine, nd = not done, P = LA in PBS, V = LA in vaseline, sc = subcutaneous application of LA, top = topical application of LA. – = negative, + = positive.

*Stimulation index (SI), **exact LA could not be identified, LTT: concentration of Ag ranged from 1 to 100 µg/mL. No Ag = background control: c.p.m. in culture, no antigen added. †Skin symptoms appeared delayed (> 2 h after injection).

All six persons of the control group had a negative intradermal skin test, negative patch test, as well as negative LTT results (SI < 2) to the battery of the nine LAs tested.

The results of patch tests and LTT suggest that allergic skin symptoms like urticaria and angioedema could be T cell-mediated in some patients who do not show evidence of an IgE-mediated reaction. In nine subjects with allergic skin reactions after the application of LA, only a T-cell sensitization could be demonstrated by the aid of patch and LTT (six positive patch, six positive LTT, 3/12 positive in both patch and LTT).

Discussion

Side-effects to LA are frequent and the symptoms following the application of LA usually are similar to IgE-mediated reactions [3,4,6]. However, only a minority of patients suffering from side-effects showed evidence – by means of positive intradermal skin tests – of an IgE-mediated reaction [2–4,6,15]. In this study we demonstrated that some patients with AR after subcutaneous application of LA showed evidence for a T cell-mediated sensitization.

We focused on patients who experienced urticaria or angioedema after LA, since these symptoms can be

objectivated and frequently appeared hours after subcutaneous application of the LA, which is not typical for the immediate type of allergic reaction due to IgE. Indeed, in the selected group of 20 subjects, only two (10%) had positive immediate skin tests to LAs. Thus, our study confirms the lack of detectable IgE to LAs in most patients experiencing AR to these drugs.

Of 20 patients analysed more in detail, 30% had a positive patch test reaction after 48 or 72 h, but only 3/6 positive patch test results correlated with the LA implicated in the AR. The relevance of the other positive skin reactions is still unclear and may represent the known limitations concerning sensitivity and specificity of epicutaneous testing [16,17]. It may represent an irritative reaction occurring in certain individuals only (since the controls were negative) or be caused by some cross-reactivity. The LTT results correlated better with the patients' history. Moreover, we could recently demonstrate the specificity of T-cell proliferation in the LTT, by generating T-cell lines and T-cell clones to lidocaine and mepivacaine [18]. Our data suggest that the LTT is a more reliable test in the diagnosis of T cell-mediated sensitivity to LAs than the skin tests. This might be due to the fact that not all LAs are available in an optimal pharmacological preparation for skin testing. In addition,

we recently showed that activated T cells recognize drugs like sulfamethoxazole or lidocaine directly, without need of prior metabolism and antigen processing [19]. As this type of drug presentation is rather labile, its detection by skin and by *in vitro* tests may be limited.

It is not quite clear how the sensitization of T cells to LA occurred in each patient. However, some patients showing angioedema or urticaria after subcutaneous application were known to react with contact dermatitis after topical application of LA. Two subjects (1 and 2, Table 3) illustrate the dependence of clinical symptoms on the way the drug is applied. Their sensitization most likely occurred via a topically applied lidocaine-containing cream. Both developed a contact dermatitis to the epicutaneous application of the relevant LA (lidocaine, mepivacaine). This contact dermatitis could be verified in our patch tests. However, if the same or structurally-related LAs were applied subcutaneously, both patients showed an angioedema after 24–36 h. Thus, the way of drug application and localization seems to be decisive for the type of symptoms evolving, being contact dermatitis if epicutaneously applied, and angioedema (and urticaria) after subcutaneous application. Moreover, we recently observed a patient with contact dermatitis to mepivacaine/lidocaine, who developed an erythema exsudativum multiforme after subcutaneous mepivacaine application [18].

The association of urticaria and angioedema exclusively to IgE, complement activation or pseudoallergic reactions has recently been questioned. An additional, possibly directly T cell-mediated reaction without evidence for the participation of IgE antibodies is feasible as revealed by recent data of peptide immunizations. In the frame of an immunization study with class 1 (HIV pol. a.a. 652–660) – and class 2 (tetanus toxin a.a. 947–967) – restricted immunogenic peptides, seven of the 13 individuals tested showed minor and transient side-effects occurring after 4–6 h [20]. Besides myalgia, fatigue and slightly elevated body temperature, two patients developed urticaria. No antibodies could be detected against these small peptides. Similarly, an immunotherapy with the Fel d 1 peptide resulted in 3–6 h delayed anaphylactic reactions in some patients, and quite a few patients had asthmatic symptoms following the peptide injection [21]. Moreover, patients with drug-induced maculopapular skin eruptions show signs of a concomitant swelling (corresponding with angioedema) and even urticarial lesions, but show only T-cell reactions by skin tests and LTT. Thus not all patients developing presumably typical clinical signs of type I allergic reactions like, i.e. urticaria and angioedema appear to have IgE-mediated or pseudoallergic reactions. One might consider a T cell-mediated immune reaction as well, particularly if it appears somewhat delayed. How T cells may cause the vascular leakiness which is probably

responsible for the clinical signs of angioedema and urticaria is still unclear. At present, it is not even known whether mast cell degranulation and histamine release are involved in these reactions.

In summary, we assume that certain angioedema- and urticaria-like symptoms appearing delayed after LA application may be T cell-mediated. Further work is needed to elucidate the exact pathomechanism of these reactions. Patients should be questioned regarding contact sensitivity to LA before obtaining the LA in any mode of application.

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References

- 1 Vrhovac B. Local anesthetics. In: Duke MNG, ed. *Meyler's Side Effects of Drugs*, 13th edn. Amsterdam: Elsevier Science Publishers BV, 1996:285–97.
- 2 McCaughey W. Adverse effects of local anesthetics. *Drug Safety* 1992; 7:178–89.
- 3 Jackson D, Chen A, Bennett CR. Identifying true lidocaine allergy. *JADA* 1994; 125:1362–6.
- 4 Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996; 97:933–7.
- 5 Munoz Bellido FJ, Bellido J, Juan JL, Moyano C, Alvarez M. Adverse reaction to bupivacaine. *Allergy* 1996; 51:515–8.
- 6 Gall H, Reichert U, Kaufmann R. Lokalanästhetika-Intoleranz auf Leitungsanästhesie mit Prilocain und Bupivacain. *Allergologie* 1992 89–91.
- 7 Schulz KH, Kasemir HD. Arzneimittelallergie. In: Fuchs E, Schulz KH, eds. *Manuale Allergologicum IV*, 3rd edn. München-Deisenhofen: Dustri-Verlag Dr Karl Feistle, 1990:45–7.
- 8 Gell PGH, Coombs RRA. The classification of allergic reactions underlying disease. In: Gell PGH, Coombs RRA, eds. *Clinical Aspects of Immunology*. Oxford: Blackwell Scientific Publications, 1963:317–37.
- 9 Curley RK, Macfarlane AW, King CM. Contact sensitivity to the amide anesthetics lidocaine, prilocaine and mepivacaine. *Arch Dermatol* 1986; 122:924–6.
- 10 Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. *Contact Dermatitis* 1991; 25:45–8.
- 11 Handfield-Jones SE, Cronin E. Contact sensitivity to lignocaine. *Clin Exp Dermatology* 1993; 18:342–3.
- 12 Schatz M. Skin testing and incremental challenge in the evaluation of adverse reactions to local anesthetics. *J Allergy Clin Immunol* 1984; 74:606–16.
- 13 Wilkinson DS, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol (Stockh)* 1970; 50:287–92.

- 14 Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy* 1996; 27:175–81.
- 15 Hodgson TA, Shirlaw PJ, Challacombe SJ. Skin testing after anaphylactoid reactions to dental local anesthetics. A comparison with controls. *Oral Surg Oral Med Oral Pathol* 1993; 75:706–11.
- 16 Fischer TJ, Hansen J, Kreilgard B, Maibach HI. The science of patch test standardization. *Immunol Allergy Clinics North Am* 1989; 9:417–34.
- 17 Schulz KH, Fuchs T. Epikutantest. In: Schulz KH, Fuchs T, eds. *Manuale Allergologicum IV*, 4th edn. München-Deisenhofen: Dustri-Verlag Dr Karl Feistle, 1993:1–39.
- 18 Zanni MP, Mauri-Hellweg D, Brander C et al. Characterization of lidocaine-specific T cells. *J Immunol* 1997; 158:1139–48.
- 19 Schnyder B, Mauri-Hellweg D, Zanni MP, Bettens F, Pichler WJ. Direct, MHC dependent presentation of the drug sulfamethoxazole to human Ab T cell Clones *J Clin Invest* 1997; 100:136–40.
- 20 Brander C, Corradin G, Hasler T, Pichler WJ. Peptide immunization in humans: a combined CD8⁺/CD4⁺ T cell-targeted vaccine restimulates the memory CD4⁺ T cell response but fails to induce cytotoxic T lymphocytes. *Clin Exp Immunol* 1996; 105:18–25.
- 21 Norman PS, Ohman JL, Long AA et al. Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med* 1996; 154:1623–8.