

Twenty Years' Experience with Anaphylaxis-Like Reactions to Local Anesthetics: Genuine Allergy is Rare



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What is already known about this topic? Nonallergic mechanisms are responsible for the vast majority of anaphylaxis-like incidents within minutes after local anesthetic (LA) injections. Allergic, presumably IgE-mediated, reactions are extremely rare and have so far been published only in case reports.

What does this article add to our knowledge? LA-induced anaphylaxis-like symptoms commonly trigger the call of emergency medical services (23.9%). The majority of these incidents, however, may be attributed to psychosomatic reactions (55.7%) or vasovagal syncope (29.6%), whereas IgE-mediated LA allergy is exceedingly rare (0.5%). Anxiety-related subjective complaints frequently (30.1%) impede the interpretation of subcutaneous provocation testing.

How does this study impact current management guidelines? A urticarial flare with/without accompanying angioedema within 30 minutes after LA injections may indicate LA allergy, but mostly occurs because of other reasons or spontaneously. Intradermal skin and subcutaneous provocation testing including the suspected LA are appropriate to identify patients with IgE-mediated LA allergy.

BACKGROUND: Anaphylaxis-like reactions occur within minutes after the application of local anesthetics (LA), most commonly during dental interventions. Impressive symptoms including respiratory distress or loss of consciousness frequently give rise to a suspicion of allergy and may prompt patients and treating physicians to refuse future LA injections.

OBJECTIVE: Nonallergic mechanisms are responsible for the majority of LA-induced immediate-type reactions. In view of the preponderance of nonallergic reactions, the question arises whether genuine LA allergy may be missed during routine testing procedures.

METHODS: We retrospectively evaluated clinical data and test results from patients referred to our allergy clinic within the past 20 years for diagnostic workup of LA-induced immediate-type reactions.

RESULTS: Of 402 evaluated patients, 29 had an episode of acute urticaria within 30 minutes after LA injections, and the remaining 373 had a history of mainly subjective cutaneous, respiratory, cardiovascular, and neurological complaints. Of the patients reporting urticaria with or without angioedema,

14 were diagnosed with a spontaneous episode of urticaria, 13 had allergic or nonallergic reactions to other agents, and 2 had IgE-mediated LA allergy. LA allergy was definitely excluded by 771 subcutaneous provocation tests with skin test negative LA, thereby demonstrating the high predictive value of negative intradermal testing.

CONCLUSIONS: Skin testing and provocative LA challenge are useful to exclude LA allergy, and this testing procedure seems to be appropriate to identify the extremely rare cases with IgE-mediated LA allergy. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2051-8)

Key words: Anaphylaxis; Challenge testing; Drug adverse reaction; Drug allergy; Drug hypersensitivity

Local anesthetics (LA) are worldwide among the most commonly administered drugs. When using correct doses and injection techniques, LA rarely cause pharmacological side effects. Anaphylaxis-like reactions within minutes after LA injections, however, may present as dangerous or even life-threatening to both patients and treating physicians and commonly trigger emergency interventions. Considering the close temporal relationship between LA injection and acute clinical symptoms including respiratory distress or even unconsciousness, the suspicion of allergy is understandable.

There are many excellent review articles on anaphylaxis-like LA reactions.¹⁻³ Clinical symptoms are almost always caused by nonallergic mechanisms, especially acute psychosomatic reactions and vasovagal (neurocardiogenic) syncope⁴⁻⁷ both of which may be triggered by pain or anxiety, for example, in the context of dental interventions. Anaphylaxis-like symptoms may also be caused by pharmacological side effects of LA or

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*Abbreviations used**BAT- Basophil activation test**LA- Local anesthetic**LTT- Lymphocyte transformation test*

epinephrine as a result of relative overdosing or accidental intravascular injection (Table I).¹ In contrast, immune-mediated, immediate-type LA allergy is considered to be extremely rare. Despite the frequent use of LA, only very few convincing case reports on presumably IgE-mediated LA allergy were published.⁸⁻¹² The authors of a recent Danish study of 162 patients with suspected perioperative allergic reactions after exposure to LA could not identify any cases of genuine LA allergy.¹³

We herein evaluate retrospective data derived from a large cohort of patients over a period of 20 years to clarify whether the enormous discrepancy between suspected and proven LA allergy is associated with a risk of missing genuine LA allergy in routine testing procedures.

METHODS

Patients

We retrospectively evaluated data of 402 patients referred to our allergy clinic from January 1997 until August 2017 for diagnostic workup of immediate-type hypersensitivity reactions within 30 minutes after LA injections. The institutional review board of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

Patient history

Data collection included documentation of age and sex, treating physician, indication for LA application, and the latency time between LA injection and onset of symptoms. Clinical complaints and symptoms were assigned to 5 organ systems, namely skin, respiratory tract, cardiovascular system, gastrointestinal tract, and central nervous system. Additional information was retrieved from treating physicians, caregivers, or emergency medical records when necessary. We additionally recorded whether the clinical reaction prompted an emergency call as well as the time interval between the incident and presentation for allergy workup.

Intradermal skin testing

Preservative-free, single-dose vials were used for intradermal and provocation testing, additional tests with preservative-containing multidose preparations were performed in selected cases. Intradermal LA skin testing was performed according to international guidelines with reading after 15 minutes; a volume of approximately 50 μ L LA solution was injected intradermally.¹⁴ Comparability and continuous quality of skin test results were ensured by the use of standardized protocols in the hands of the same medical assistants over a period of 20 years (see also the Acknowledgments section). Dilutions of 1:10 of the original LA in physiological saline solution were used for routine or "screen" intradermal testing (Table II). Further dilutions, that is, 1:100 and 1:1000, were tested in the case of positive results. Positive skin reactions at the "screen" concentration of 1:10 were considered as "irritative" if subsiding on further dilution. Wheal-and-flare reactions persisting at dilutions of 1:100 were assessed as "allergic."

TABLE I. Pharmacological side effects of LA and epinephrine as differential diagnosis of anaphylaxis

LA side effects: excitement reaction	Agitation, tinnitus, dysgeusia (metallic taste), dizziness, confusion, muscle twitching, convulsions
	Erythema, flushing, sweating, nausea, vomiting
	Cardiovascular: tachycardia, hypertension
LA side effects: paralysis reaction	Motoric and sensory paralysis, loss of consciousness, respiratory arrest
	Cardiovascular: hypotension, arrhythmia (bradycardia, atrioventricular block), cardiac arrest
	Loss of sphincter control (defecation, urination)
Epinephrine side effects	Pallor, sweating, agitation, tachycardia, hypertension, thoracic pain

LA, Local anesthetic.

Laboratory testing

Since 2004, baseline serum tryptase concentrations were determined using UniCAP Tryptase (ThermoFisher Scientific, Freiburg, Germany) according to the manufacturer's instructions in selected patients with a history of severe reactions, such as loss of consciousness. Additional lymphocyte transformation test (LTT) and basophil activation test (BAT) with LA (articaine, mepivacaine, prilocaine) were performed in 2 patients with genuine LA allergy as described elsewhere^{15,16} using concentrations of 1.0, 0.1, and 0.01 mg/mL.

Subcutaneous provocation testing

Provocation tests were routinely performed in skin test negative patients as the gold standard to definitely exclude LA allergy. Depending on the patients' history, comorbidities, and individual risk profile, provocation tests were carried out in an outpatient or inpatient context. An intravenous cannula was installed to ensure immediate emergency intervention. Single-blinded placebo testing using incremental volumes of physiological saline solution was performed in 154 cases. Subcutaneous LA injections in therapeutic concentrations, for example, 10 mg/mL articaine, 10 mg/mL mepivacaine, or 10 mg/mL lidocaine, were administered every 30 minutes at increasing amounts of 0.1, 0.2, 0.5, 1.0, and 2.0 mL into the outside of the upper arm, yielding a cumulative dose of 3.8 mL (=38 mg). Only 1 LA was given per day. Patients were observed for at least 1 hour after the last injection.

Definitive diagnosis

The final diagnosis was based on an overall assessment including history, clinical complaints, and symptoms as well as the results of intradermal and provocation testing.¹ Shortness of breath along with palpitations and acral/perioral paresthesia was considered typical of hyperventilation or a panic attack. Sweat eruptions combined with nausea, dizziness, and/or bradycardia were considered to be indicative of a vasovagal reaction. Differential diagnoses of spontaneous urticaria, laryngospasm, nonallergic drug hypersensitivity reactions, drug allergy, and latex allergy were based on published consensus criteria.¹⁷⁻²¹ All medical records and final diagnoses were monitored by the institutional head allergist (AT) to ensure consistent quality and plausibility.

TABLE II. Intradermal skin testing: LA concentrations and test results

LA group	LA	Original conc. (mg/mL)	1:10 routine intradermal test conc. (mg/mL)	Test reactions		
				Negative	Irritative	Allergic
Benzoic acid ester	Procaine	10.0	1.0	201	12	0
Amides	Mepivacaine	10.0	1.0	394	5	1
	Bupivacaine	5.0	0.5	66	1	0
	Lidocaine	10.0	1.0	394	0	0
	Prilocaine	20.0	2.0	24	0	1
	Articaine	10.0	1.0	394	17	2

LA, Local anesthetic.

TABLE III. Clinical data including signs and symptoms of LA-induced reactions

No. of patients	Total (n = 402)	Females (n = 316)	Males (n = 86)
Median age (range)	50 (3-86)	50 (3-86)	47 (5-83)
Incriminated LA			
Articaine	185	150	35
Mepivacaine	81	62	19
Lidocaine	57	47	10
Prilocaine	24	16	8
Procaine	16	13	3
Other	24	14	10
Unknown	15	14	1
Latency time from LA administration to first symptoms			
< 1 min	54	42	12
1-5 min	213	170	43
6-15 min	64	53	11
16-30 min	71	51	20
Symptoms			
Cutaneous			
Paresthesia, pruritus	88	72	16
Pallor, sweating, heat sensation, chills	134	106	28
Flushing, erythema	47	38	9
Urticaria with/without angioedema	29	19	10
Upper respiratory			
Throat tightness, globus sensation	139	121	18
Stridor, cyanosis	6	4	2
Lower respiratory			
Chest tightness, dyspnea	163	141	22
Wheezing, cyanosis	1	0	1
Cardiovascular			
Palpitations, tachycardia	177	148	29
Hypotension	85	57	28
Shock or cardiac arrest	3	2	1
Gastrointestinal			
Mild abdominal pain	87	68	19
Nausea, vomiting	15	13	2
Loss of sphincter control	6	3	3
CNS			
Malaise, agitation, anxiety	108	95	13
Dizziness, visual disturbances, hearing impairment	158	135	23
Somnolence, syncope (loss of consciousness)	115	74	41

CNS, Central nervous system; LA, local anesthetic.

TABLE IV. Basal serum tryptase values, results of provocation testing and final diagnosis

	Total (n = 402)	Females (n = 316)	Males (n = 86)
Time interval between LA reaction and allergy workup (y)			
<1	200	158	42
1-5	106	90	16
>5 but <10	16	12	4
>10	55	40	15
Not documented	25	16	9
Basal serum tryptase values (ng/mL)			
Minimum	1.06	1.06	1.39
Maximum	22.40	14.10	22.40
Mean	4.51	4.18	5.88
<5.00	86	73	13
≥5.00 but <10.00	31	22	9
≥10.00	5	3	2
Not done	280	218	62
LA provocation			
Articaine	314	252	62
Mepivacaine	251	204	47
Lidocaine	89	71	18
Procaine	45	32	13
Prilocaine	36	23	13
Bupivacaine	32	24	8
Other	4	2	2
Results of LA provocation testing			
Negative	281	206	75
Subjective complaints	121 (30.1%)	110 (34.8%)*	11 (12.8%)*
Final diagnosis			
Psychosomatic reactions: hyperventilation, panic attack	224 (55.7%)	196 (62.0%)*	28 (32.6%)*
Vasovagal (neurocardiogenic) syncope	119 (29.6%)	82 (25.9%)*	37 (43.0%)*
LA side effects	15	10	5
Spontaneous urticaria	14	11	3
LA-independent allergic or nonallergic reactions	13	8	5
Epinephrine side effects	10	5	5
Laryngospasm	5	4	1
LA allergy	2	0	2

LA, Local anesthetic.

*Statistically significant differences between females and males (see also the Results section).

Statistics

Statistical analyses were performed with SPSS version 24 for Windows (SPSS Inc., Chicago, Ill). The χ^2 test was performed to compare male and female patients for categorical data.

RESULTS

Clinical data

Medical records of 402 patients with a history of anaphylaxis-like symptoms occurring within 30 minutes after the administration of LA were evaluated. LA were most commonly given by dentists (224×), occasionally by orthopedists (69×), surgeons (38×), dermatologists (27×), or otolaryngologists (16×). Accordingly, the main indications for LA were dental interventions (223×), treatment of dorsal pain (61×), peripheral nerve blockades (53×), and skin surgery (51×). Table III shows baseline clinical data including the patients' age and sex, incriminated LA, time interval to onset of symptoms, and clinical signs. In view of the

predominance of females (78.6%), data on women and men are depicted separately. A call of emergency medical services was found to be required by the treating physician in 96 cases (23.9%). The time interval between the LA-associated reaction and presentation for allergy workup ranged from less than 1 year (49.8%) to more than 10 years (13.7%, Table IV).

Intradermal skin testing

A standard panel of LA consisting of articaine, lidocaine, and mepivacaine was tested in 168 patients. Additional LA were tested according to the patients' history (1 additional LA in 160 patients, 2 additional LA in 47, and 3 additional LA in 19), for example, the benzoic acid ester procaine (201×) and/or the amides bupivacaine (66×) and prilocaine (24×). Skin testing could not be evaluated in 3 patients because of urticarial dermographism. Intradermal testing at the routine or "screen" dilutions of 1:10 was positive in 24 of total 402 patients, meaning that a wheal-and-flare reaction exceeding 5 mm was

TABLE V. History and diagnostic results in 2 cases of genuine LA allergy

LA	Intradermal test conc. (mg/mL) and dilution levels	Wheal diameter (mm)	Results of subcutaneous provocation testing
Case 1 (28 y, male): urticaria and hypotension 5 min after dental articaine injection (3 mo before)			
Articaine	1.0 (1:10)	14	n.d.
	0.1 (1:100)	11	
	0.01 (1:1000)	11	
Mepivacaine	1.0 (1:10)	7	Tolerated
	0.1 (1:100)	—	
Prilocaine	2.0 (1:10)	—	Tolerated
Procaine	1.0 (1:10)	—	Tolerated
Case 2 (34 y, male): urticaria, angioedema, and tachycardia 20 min after dental articaine injection (12 y before)			
Articaine	1.0 (1:10)	12	n.d.
	0.1 (1:100)	9	
	0.01 (1:1000)	—	
Mepivacaine	1.0 (1:10)	7	n.d.
	0.1 (1:100)	9	
	0.01 (1:1000)	—	
Prilocaine	2.0 (1:10)	12	n.d.
	0.2 (1:100)	10	
	0.02 (1:1000)	—	
Procaine	1.0 (1:10)	—	Tolerated

LA, Local anesthetic; n.d., not done.

documented for at least 1 LA (Figure 1; Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In only 2 of these 24 patients positive test reactions were confirmed on further dilution to 1:100 (Figure 1; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The calculated diagnostic sensitivity of intradermal testing at LA dilutions of 1:10 was 100%, and the specificity 94.5%. LA-specific intradermal test results are summarized in Table II.

Laboratory testing

Baseline serum tryptase concentrations were available for 122 patients, most of whom had values of less than 10 ng/mL (95.9%), or even less than 5 ng/mL (70.5%, Table IV). Within the entire patient series, only one case of systemic mastocytosis with a basal serum tryptase value of 22.40 ng/mL was diagnosed according to published criteria.²² Additional BAT and LTT in the 2 patients with genuine LA allergy failed to reveal any positive test results.

Subcutaneous provocation testing

Provocation tests with skin test negative LA were performed in all 402 patients. More than 1 LA was given in 320 cases (79.6%), resulting in a total of 771 provocation tests. Subcutaneous provocation was tolerated without incident in the majority of patients (n = 281; 69.9%). A significant proportion (n = 121; 30.1%), however, complained of subjective symptoms resembling the initial LA-induced reaction, for example, shortness of breath, paresthesia, palpitations, and dizziness. Subjective complaints were significantly more frequent in female compared with male patients (34.8% vs 12.8%; $P < .001$). Symptoms were invariably mild and improved after reassurance of the patient and symptomatic therapy. No anaphylactic reactions to skin test negative LA were observed.

Definitive diagnosis

Considering documented and self-reported symptoms after LA injections and the outcomes of subcutaneous provocation testing, an acute psychosomatic reaction was retrospectively diagnosed in 224 patients, whereas a neurocardiogenic syncope was found to be most likely in 119 cases. Psychosomatic reactions were significantly more common in female patients ($P < .001$), whereas vasovagal syncope was more frequent in men ($P = .003$). Clinical symptoms and the way of application/dosage of the suspect LA (with or without epinephrine) were indicative of pharmacological side effects in 25 cases: 15 were attributed to LA toxicity, and 10 to epinephrine. Acute urticaria with or without accompanying angioedema was documented in 29 cases. Fourteen were retrospectively classified as acute spontaneous urticaria, and 13 as allergic or nonallergic hypersensitivity reactions to various agents (Table IV). The latter included nonallergic hypersensitivity to nonsteroidal anti-inflammatory drugs (2× diclofenac, 1× ibuprofen) or atracurium (3×) as well as IgE-mediated allergy to cephalosporins (2× cefazolin, 1× ceftriaxone), latex (2×), gelatine (1×), or metamizole (1×). Acute laryngospasm presumably triggered by oropharyngeal medical interventions was considered the most likely diagnosis in 5 patients.

Allergy cases

Clinical data of the 2 patients diagnosed with genuine, presumably IgE-mediated, LA allergy are shown in Table V; patient 1 was published previously as a case report.¹¹ Both were young men, had baseline serum tryptase concentrations within the normal range (4.95 and 2.61 ng/mL, respectively), and had a history of urticarial skin reactions shortly after injection of articaine, which were accompanied by hypotension and tachycardia. An isolated allergy to articaine was confirmed in patient 1 by positive intradermal testing; skin and subcutaneous provocation tests with mepivacaine, prilocaine, and procaine were negative.

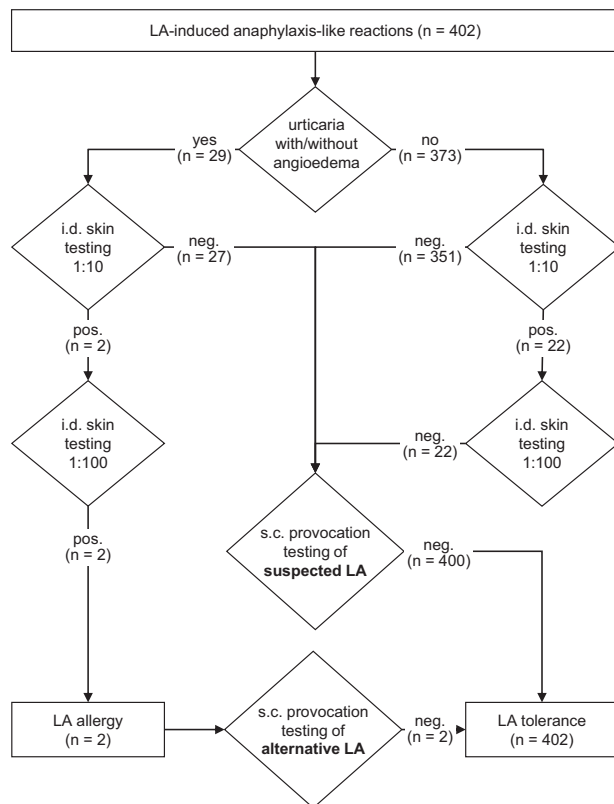


FIGURE 1. Results of allergy workup in patients with or without urticaria during LA-induced anaphylaxis-like reactions. *i.d.*, Intradermal; LA, local anesthetic; *s.c.*, subcutaneous.

Intradermal skin testing demonstrated cross-reactivity to all other amide LA tested in patient 2; only procaine was tolerated in intradermal and subsequent subcutaneous provocation tests. Further dilution of LA preparations for intradermal skin testing seemed to decrease sensitivity as intradermal test results for all LA became negative at dilutions of 1:1000 in patient 2.

DISCUSSION

In view of the extensive use of LA, IgE-mediated allergy is an exceedingly rare complication. In our cohort of 402 patients who were referred for allergy workup of LA-induced anaphylaxis-like incidents over a period of 20 years, test results were found to be compatible with IgE-mediated LA allergy in only 2 cases (Figure 1). Pain and/or anxiety are commonly considered as predisposing factors for LA reactions mimicking anaphylaxis. We accordingly found that most reactions occurred in the context of dental interventions (55.5%) or during orthopedic LA injections for the treatment of back or joint pain (15.2%). Most incidents (55.7%) were attributed to acute psychosomatic reactions (panic attacks, hyperventilation), or vasovagal (neurocardiogenic) syncope (29.6%), whereas the toxic effects of LA or epinephrine were considered the most likely cause in 3.7% and 2.5%, respectively. Regardless of their origin, LA-induced acute incidents may present as dramatic or even life-threatening situations. In our cohort, a call of emergency medical services was deemed necessary by the treating physician in 23.9% of the cases.

A total of 162 patients with presumably LA-induced allergic reactions in the course of major surgical interventions were evaluated in a recent study by Kvisselgaard et al¹³; 86 of these incidents occurred during general anesthesia, and the remaining 76 took place in awake patients. The majority of patients included in our current study had suffered LA-related incidents in the context of minor outpatient procedures. The comparability between both studies is thus limited. Psychosomatic reactions and vasovagal syncope do not represent relevant differential diagnoses during general anesthesia. Even during the perioperative observation of awake patients, the rate of unspecific cerebral symptoms/dizziness was relatively low in the Danish cohort (7.9%) as compared with our current observations (39.3%). We likewise found a higher rate of syncope/loss of consciousness (28.6% vs 6.6%). The most important difference between the 2 studies, however, is our identification of 2 patients with IgE-mediated LA allergy. We hereby demonstrate that genuine IgE-mediated allergy to LA, though very rare, is still an important differential diagnosis to be kept in mind. Kvisselgaard et al found a significantly higher rate of IgE-mediated allergic reactions to other allergens (32.1% vs 1.7% in our group), most commonly to chlorhexidine (12×), cefuroxime (8×), and the patent blue dye (7×). The observed difference is likely to be due to the context of major surgical interventions and thus exposure to a variety of potential allergens in Kvisselgaard's cohort.

Acute psychosomatic reactions, that is, hyperventilation or panic attacks, the most common cause of LA reactions, frequently occur during or immediately after injections.²³ Symptoms include palpitations, acral/perioral paresthesia, tremor, dry mouth, perception of heat or cold, respiratory distress, weakness, or drowsiness.²⁴ The observation that anxiety-related disorders are at least twice as common in women as in men^{25,26} might at least partially explain the pronounced predominance of females (78.6%) in our patient cohort. Accordingly, an acute psychosomatic reaction was considered to be the most likely cause of the LA-associated incident in 62.0% of women, but only 32.6% of men ($P < .001$). Moreover, anxiety-related subjective symptoms during provocation testing were significantly more frequent in female patients (34.8% vs 12.8%; $P < .001$, Table IV). Anxiety-related symptoms during provocation testing occasionally present as acute, dramatic events and may therefore be misinterpreted as anaphylactic, thus "positive" test reactions by both patients and inexperienced physicians.

Vasovagal (neurocardiogenic) syncope as the second leading cause of LA-related adverse events is commonly preceded by a prodromal phase including sweating, nausea, and dizziness.^{27,28} Notably, both psychosomatic reactions and vasovagal syncope may be accompanied by a variety of cutaneous symptoms such as pruritus, sweating, flush or pallor, and sensations of heat and cold, which may mislead laypersons and medical staff to suspect an allergic reaction. Generalized urticaria with/without angioedema, however, does not belong to the spectrum of psychosomatic and vasovagal reactions.

LA-related pharmacological side effects and toxicity are dose dependent and more likely to occur on accidental intravascular injection. Subgroups of patients, however, might be predisposed to develop pharmacological side effects at lower doses.²⁹ In our cohort, LA toxicity was suspected in 15 patients who developed compatible symptoms shortly after administration of high doses of LA. LA preparations for dental surgery frequently contain

epinephrine as a vasoconstrictor. The doses administered are generally considered to be too low to cause systemic side effects in healthy individuals.³⁰ Predisposing comorbidities such as hyperthyroidism, arterial hypertension, and/or cardiac conditions, however, might individually increase sensitivity to epinephrine.

Both patients with genuine LA allergy had a history of generalized urticaria accompanied by arterial hypotension and tachycardia within 5 to 20 minutes after LA injections. Interestingly, no cutaneous symptoms were documented at the actual LA injection site. This is in accordance with case reports describing generalized cutaneous and systemic symptoms, but no accentuation at the injection site.^{12,31,32} We conclude that LA-associated acute episodes of urticaria/angioedema are to some extent indicative of genuine LA allergy (Figure 1). The positive predictive value of this single clinical sign, however, is low, as urticaria is more frequently caused by other drugs and may also occur spontaneously.

At present, IgE-mediated LA allergy can neither be diagnosed nor excluded by laboratory tests.^{1,33} LA-specific IgE measurement is not validated, and BAT remains an experimental tool with unknown diagnostic sensitivity and specificity.³⁴ In view of data derived from venom allergic patients, an association of anaphylaxis-like LA reactions with elevated baseline serum tryptase values has been suggested.^{35,36} As previously published for the context of nonsteroidal anti-inflammatory drug hypersensitivity,³⁷ mean serum tryptase concentrations in our present cohort were comparable with those of the general adult population (4.51 and 5.60 ng/mL, respectively).³⁸

In accordance with our present findings, case reports of LA-induced anaphylaxis suggest a high diagnostic sensitivity of intradermal skin testing. The actual rate of false negative skin test results is unclear, and subcutaneous provocation testing remains the gold standard to definitely exclude LA allergy.^{1,33,39,40} Moreover, the psychological benefits of tolerated provocation testing may enable patients (and treating physicians) to accept future therapeutic administration of LA. Although provocation tests should invariably include the (skin test negative) incriminated substance, 1 or 2 additional LA may be administered for proof of tolerability according to the request of patients or treating physicians. As another advantage, provocation testing with more than 1 substance permits a single-blinded approach. Subcutaneous administration of physiological saline solution as a placebo control may be considered for anxious patients with a high likelihood of anxiety-related subjective reactions.⁴¹ Because of the lack of time and resources in a routine diagnostic setting, placebo testing could be performed only in a limited number of selected cases. Moreover, placebo testing is limited by the lack of an anesthetic effect that impedes blinding of the patient. In our cohort, 121 patients experienced subjective complaints during the course of LA provocation, most of which were classified as acute psychosomatic reactions resembling the initial episode.

CONCLUSIONS

1. Within the group of patients with acute LA-mediated incidents, a history of LA-associated episodes of acute urticaria/angioedema appears to identify individuals with a certain degree of risk of IgE-mediated LA allergy.
2. Intradermal skin testing with LA dilutions of 1:10 has a specificity of 94.5% and may therefore produce false

positive test reactions. Positive test results with 1:10 diluted LA solutions need to be verified by additional testing of 1:100 dilutions. Consequently, allergists can perform intradermal LA skin testing only with 1:100 diluted LA solutions.

3. The predictive value of negative LA skin testing seems to be close to 100% because we have seen no objective anaphylactic reactions during subcutaneous provocation testing in skin test negative individuals.
4. Anxiety-related subjective complaints frequently occur during subcutaneous provocation testing with LA and may impede its interpretation.

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TABLE E1. Two $\times$ two table depicting the results of routine or “screen” intradermal testing in all 402 patients using 1:10 dilutions of the original LA concentration

	Patients with LA allergy	Patients with LA tolerance*	Total
Intradermal testing (1:10)			
Patients with positive results	2	22	24
Patients with negative results	0	378	378
	2	400	402

LA, Local anesthetic.

*Determined by negative subcutaneous provocation testing.

TABLE E2. Two $\times$ two table depicting the results of additional intradermal testing using 1:100 dilutions of the original LA concentration in case of 24 patients with test reactions to the routine or “screen” concentration of 1:10

	Patients with LA allergy	Patients with LA tolerance*	Total
Intradermal testing (1:100)			
Patients with positive results	2	0	2
Patients with negative results	0	22	22
	2	22	24

LA, Local anesthetic.

*Determined by negative subcutaneous provocation testing.