

Risk of Immediate-Type Allergy to Local Anesthetics Is Overestimated—Results from 5 Years of Provocation Testing in a Danish Allergy Clinic



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What is already known about this topic? Immediate-type allergy to local anesthetics (LAs) is considered rare by allergists. However, many health care professionals and patients still overestimate the risk of immediate-type LA allergy and potential cross-reactivity.

What does this article add to our knowledge? Immediate-type allergy to LAs is extremely rare. Reactions most commonly have another nonallergic mechanism such as vasovagal reactions, or are caused by other simultaneous exposures such as chlorhexidine and latex, which should always be coinvestigated.

How does this study impact current management guidelines? Skin testing with LAs may be false positive and should always be followed by subcutaneous provocation. Low-risk patients may be managed with placebo-controlled subcutaneous provocation with the culprit LA without prior skin testing.

BACKGROUND: Local anesthetics (LAs) are used in many health care settings and exposure during a lifetime is almost inevitable. Immediate-type allergy to LAs is considered rare among allergy experts but is commonly suspected by health care workers from other specialties, and by patients.

OBJECTIVE: The main aim of this study was to investigate the incidence of immediate-type allergy to LAs in our regional allergy clinic over the 5-year period 2010 to 2014.

METHODS: This was a retrospective single-center study of patients referred to a regional allergy clinic (excluding patients with perioperative reactions) with suspected immediate allergy to LAs, who had undergone subcutaneous provocation with 1 or more LAs. Patients were identified in the hospital clinical coding system and clinical information about the reaction and investigation results was obtained from their medical records.

RESULTS: A total of 164 patients (123 women/41 men; median age, 56 years; range, 7-89 years) who had 189 provocations with LAs were included over the 5-year period 2010 to 2014. All 164 patients had negative subcutaneous provocations to all 189 tests

with LAs (95% CI, 0%-1.83%). Another allergen was identified in 10% (n = 17) of the patients.

CONCLUSIONS: None of the 164 patients with suspected immediate-type allergy to LAs reacted on provocation. Thus, no patients have been diagnosed with an immediate allergy to LAs in our regional allergy clinic in the 5-year period studied, and allergy to LAs must be considered very rare. Alternative mechanisms should be considered, but if symptoms are consistent with allergy, other potential allergens should be investigated. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1217-23)

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Local anesthetics (LAs) are widely used in the health care profession, in both primary care and dentistry and across all hospital specialties. Worldwide approximately 6 million doses of LAs are administered daily.¹ Most LA consumption is in the injectable form used by dentists, general practitioners, emergency departments, hospitals, or other specialists' clinics before minor or major painful procedures. Transdermal/mucosal administration of LAs is found in creams/gels to treat burns, insect stings, and itching, as well as in topical analgesia before painful procedures such as venepuncture and dental procedures, especially among pediatric patients.

Immediate-type allergic reactions to LAs are considered rare among allergy experts, but the risk is still overestimated by health care workers from other specialties, and not least by patients, leading to unnecessary avoidance of LAs. Earlier studies suggest an incidence of immediate allergy to LAs in the range of 0% to

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Abbreviations used

IDT- intradermal test

IR- immediate reaction

LA- local anesthetic

NIR- nonimmediate reaction

SCP- subcutaneous provocation

SPT- skin prick test

1.12%²⁻⁷ after allergy investigation. A recent study of a cohort of patients with allergic reactions in the perioperative setting investigated by our group has shown that in 10 years of systematic investigations not a single patient tested positive to LAs.⁸

Allergy comprises only 2.5% to 10% of all adverse drug reactions to LAs.⁹ Adverse drug reactions are more frequently associated with nonallergic causes, for example, toxicity with paresthesia and dizziness due to relative overdose or vasovagal reactions manifested as hypotension and bradycardia. Finally, the pharmacological effect of added vasopressors, for example, adrenaline, can cause tachycardia, palpitations, and hyperventilation. All the above reactions present without skin symptoms. On the other hand, reactions presenting with symptoms from the skin such as urticaria or flushing, and/or respiratory and circulatory symptoms, are more indicative of an allergic mechanism. Recently, it has been suggested that allergy to LAs is less common than allergy to other drugs/substances administered simultaneously or to other ingredients in the LA solution (eg, excipients).^{3,10}

No, or insufficient, investigation of a suspected allergic reaction to LAs may cause unnecessary avoidance of LAs. Avoidance may cause discomfort to the patient and can lead to painful procedures, for example, root canal surgery or coronary angiography being delayed, or performed either without anesthesia, or in general anesthesia, at increased risk to the patient.¹¹

The Allergy Clinic at Copenhagen University Hospital, Gentofte, is the Capital Region's only highly specialized allergy department covering a population of approximately 2 million inhabitants. Most of the region's drug allergy cases are referred to the department.

The main aim of this study was to investigate the incidence of immediate-type allergy to LAs in our regional allergy clinic over the 5-year period 2010 to 2014. The present study does not include patients with reactions in the perioperative setting because the results from this cohort have been published previously.⁸

METHODS

All patients undergoing investigation in the allergy clinic with subcutaneous provocation (SCP) with LAs in the period January 2010 to December 2014 were retrospectively included in the study. The allergy clinic mainly investigates adults, but since 2013 children (>6 years) with suspected drug allergy have also been investigated. Patients are referred by general practitioners, specialists, or hospital departments. The study was approved by the Danish Health and Medicines Authority (reference no. 3-3013-1068/1).

The hospital's clinical coding system was used to identify patients who had been tested with SCP to LAs. Patients with perioperative reactions were excluded from this study. In Denmark all citizens are registered in the Civil Registration System, which makes it possible to cross-reference patients between the coding system and their respective medical records.

Data were collected from patients' medical records by the first author. Information regarding symptoms, culprit drug, location at time of reaction, and treatment was collected when recorded by the doctor. No assumptions or clinical interpretations were made about information not specifically mentioned.

Patients were included if they had been tested with SCP for a suspected immediate reaction (IR) to LAs. An IR was defined as a reaction with rapid onset (within minutes/few hours of exposure) and symptoms such as urticaria, bronchospasm, dizziness/fainting, or anaphylaxis.¹² Patients without suspected reactions or with a history of a nonimmediate reaction (NIR) were excluded. A non-immediate reaction was defined as a reaction with delayed presentation (several hours/days after exposure) causing only skin symptoms, for example, eczema or maculopapular exanthema.¹²

All patients with suspected IR to LAs underwent individualized investigations with 1 or more suspected LA. The investigation program was planned on the basis of an individual risk assessment including the following: history consistent with allergy, reaction severity, comorbidity, and expected level of psychological involvement.

Subcutaneous provocation is considered the criterion standard¹³ and was carried out as a titrated provocation if the procedure was considered at high risk of resulting in a reaction, such as reactions with symptoms suggestive of allergy, severe reactions, and/or severe comorbidity. A single full-dose provocation was planned if the procedure was considered at low risk of resulting in a reaction, such as reactions with no symptoms suggestive of allergy, mild reactions, and no comorbidity. Both provocation types were single-blinded and placebo-controlled.¹⁴ Titrated provocations comprised an NaCl placebo injection followed by LA doses of 1/100, 1/10, and 1/1 with 45-minute intervals. Full-dose provocations were carried out with an NaCl placebo injection and LA dose 1/1. Patients were tested with up to clinical doses (see Table I). A provocation was considered positive on the development of objective allergy symptoms, that is, skin symptoms (rash/swelling) and/or respiratory/circulatory symptoms within 2 hours of provocation.

As a rule, the culprit drug was tested, but in cases in which the culprit drug was unknown, patients were tested with either lidocaine or an LA requested for an upcoming procedure. Other potential allergens from the time of reaction such as antibiotics, analgesics, latex, glucocorticoids, and disinfectants were tested in some cases, but not systematically. Other allergens were identified from the history, relevant notes, and charts and were investigated according to local guidelines.

Patients were not routinely skin tested before provocation. When used, skin prick tests (SPTs) and intradermal tests (IDTs) were performed¹⁵ and interpreted as described earlier.⁸ Dilutions of LAs used for SPT and IDT are presented in Table I.

Statistical analysis

Categorical variables were cross-tabulated using Fisher exact test to examine subgroups. For continuous variables, logarithmic transformation with independent-sample *t* test was used. Statistical significance was defined as a *P* value of less than .05.

All statistical tests were carried out in RStudio version 0.99.892 and descriptive data analyzed in Microsoft Excel 2010 version 14.0.7162.5.

RESULTS

A total of 5,076 drug provocations were performed in the Allergy Clinic during the 5-year period (Figure 1). Only 207 of

TABLE I. Maximum doses for skin tests and SCPs

LA	SPT (mg/mL)	IDT (mg/mL)	SCP (mg)
Lidocaine	20	20	40
Mepivacaine	10	10	40
Bupivacaine	2.5	2.5	5
Ropivacaine	7.5	7.5	75
Prilocaine	30	30	45
Articaine	40	4	60

these were LA provocations (4%) carried out in a total of 180 patients, including 8 pediatric patients. Patients without a suspected allergic reaction ($n = 4$) were excluded. Furthermore, 8 patients were excluded on the basis of a history of suspected nonimmediate reactions to LAs.

A total of 168 patients (127 women/41 men; median age, 56 years; range, 7-89 years) including 8 pediatric patients with histories of IR to LAs (5 girls/3 boys; median age, 10.5 years; range, 7-17 years) were tested with 195 provocations to LAs.

Provocations were titrated in 101 (52%) cases, full dose in 63 (32%) cases, and not specified in 16% of the cases. Provocations were performed with lidocaine ($n = 123$ [63%]), mepivacaine ($n = 25$ [13%]), articaine ($n = 16$ [8%]), prilocaine ($n = 15$ [8%]), bupivacaine ($n = 14$ [7%]), and ropivacaine ($n = 2$ [1%]). Of the patients with a suspected IR to LAs, 131 (78%) were tested with the culprit LA. Among 28 (17%) patients, the culprit drug was unknown and 9 (5%) patients were tested only with an alternative LA.

As shown in Figure 1, 2 patients were excluded after provocation because of chronic allergy symptoms continuing during provocation. In addition, 2 patients experienced symptoms not consistent with allergy and were excluded.

Thus, in total 164 patients were included and they all had negative SCP to all 189 tested LAs (95% CI, 0%-1.83%). Only 12% of the patients were skin tested and all test results were negative. Among these, 7 patients were tested with SPT only and 13 patients with SPT and IDT.

Symptoms attributed to vasopressors, such as tachycardia, palpitations, and dizziness without skin symptoms, were observed during SCP in 7% ($n = 12$) of the patients. Another allergen was confirmed in 10% ($n = 17$) of the patients. The following allergens were confirmed on investigation: antibiotics ($n = 7$), acetylsalicylic acid ($n = 3$), diclofenac ($n = 2$), glucocorticoid ($n = 2$), latex ($n = 1$), sodium hypochlorite ($n = 1$), and contrast media (Iomeprol, $n = 1$).

Because all included patients tested negative on SCP with LA, clinical characteristics could not be differentiated between LA-allergic and LA-nonallergic patients. The clinical characteristics of the 164 patients testing negative following suspected IR to LAs are illustrated in Table II. Comparison is made between patients testing negative to LAs (no allergen group) and patients testing negative to LAs, but positive to another allergen (other allergen group). Information about airway and circulatory symptoms was collected, but inconsistently documented and is therefore not included.

There were no significant differences in patients' demographic characteristics (age, sex, or location at the time of the reaction) between the groups. In patients in whom an allergic reaction was ruled out, most reactions took place at the dentist. Among

patients in whom another allergen was found, most reactions occurred in hospitals.

There was no significant difference in reported cerebral symptoms, which were reported in 35% of the patients in whom another allergen was confirmed and 57% of the patients in the no allergen group. However, patients with another allergen were significantly more likely to have skin symptoms in addition to cerebral symptoms ($P = .001$).

The presence of skin symptoms was well documented in both groups and was significantly more frequent in the other allergen group (16 of 17 vs 49 of 147; $P > .001$). In the other allergen group, all but 1 had skin symptoms and more than two-third were generalized. In contrast, in the no allergen group, only one-third had skin symptoms and only one-fourth were generalized. The exact character of skin symptoms was inconsistently reported and thus it was chosen not to report other detail than generalized versus localized.

Treatment for the suspected reaction was not systematically documented. However, all patients with another allergen had been treated with antihistamines compared with less than two-third of the patients for whom no allergen was found. The same applied to treatment with glucocorticoids for which more than 80% were treated with glucocorticoids in the other allergen group versus less than half in the no allergen group. There was no difference in the use of adrenaline between the 2 groups although numbers were small.

Identifying NIRs was not a main aim of the study, but 1 of the included patients presented with an NIR 2 days after a negative SCP had excluded immediate LA allergy. None of the 8 patients excluded because of a suspected NIR to LA had an immediate reaction on SCP. However, 2 of these patients developed an NIR to SCP (see Figure 1).

DISCUSSION

No patients have been diagnosed with IR to LAs in our large regional allergy clinic over the 5-year period 2010 to 2014. All 164 patients with suspected IR to LAs tested negative on SCP with LAs, and allergy to LAs must be considered very rare. IR to LAs are also rarely reported in the literature; a recent review found the incidence to be less than 1%.¹⁶ In larger studies with more than 100 patients with suspected reactions to LAs who were tested with the culprit LA, the incidence was 0% to 1.12%.²⁻⁷ In a different cohort of perioperative patients investigated in the Danish Anaesthesia Allergy Centre, no LA-allergic patients (95% CI, 0%-1.8%) were identified over a 10-year period. Extrapolating these figures the incidence was suggested to be less than 1:1.2 million anesthetized patients.⁸ Regardless of these studies, the risk of allergic reactions to LAs continues to be overestimated by health care personnel and patients leading to significant morbidity.¹¹

The low molecular weight (200-300 Da) of LAs make them incomplete allergens, that is, haptens. Haptens are dependent on the host's ability to make hapten-protein complexes necessary to induce IgE-antibody production. It is still uncertain which hapten-protein complexes are formed by LAs.¹⁷ A low tendency to form such complexes may explain the low rate of IR to LAs.

Most patients did not have skin symptoms during the suspected reaction and those presenting with generalized skin symptoms were more likely to have reacted to another allergen. Investigations revealed another allergen in 10% of the patients

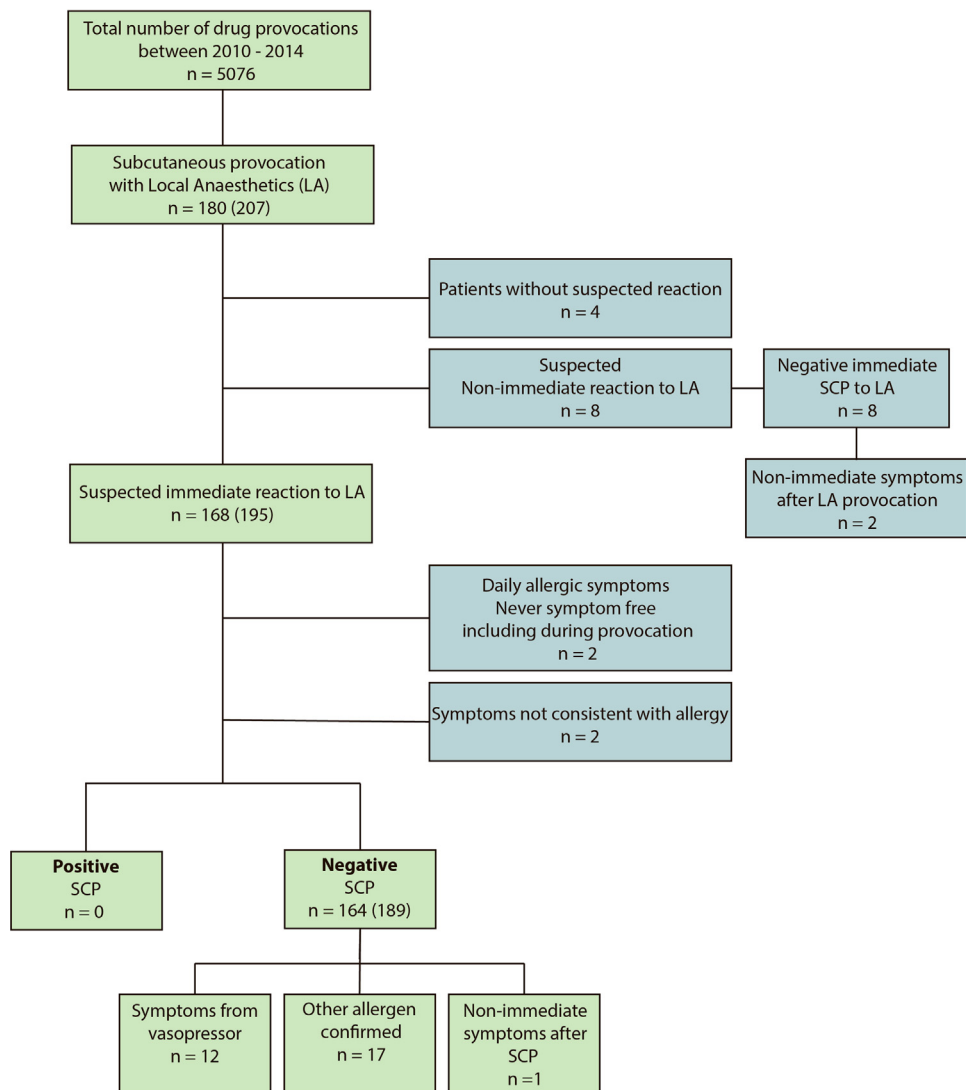


FIGURE 1. Flowchart of patients investigated for LA allergy. n = number of patients; (n) = number of drugs tested.

tested with the suspected LA. The most frequent allergens were antibiotics, analgesics, and coadministered glucocorticoids. One patient tested positive for latex. Cerebral symptoms such as dizziness or fainting were frequently reported especially among patients in whom no allergen was found. When only cerebral symptoms were present, most patients experienced spontaneous recovery shortly after the reaction. There are several possible causes of cerebral symptoms: Mental discomfort and anxiety can cause vasovagal syncope, and additional cerebral symptoms can occur because of hyperventilation induced by anxiety, by the effects of the vasopressor, or because of toxic effects of LA caused by inadvertent intravascular injection. In patients presenting with predominantly cerebral symptoms, without skin symptoms, an allergic mechanism is less likely.

Further education in how to recognize anaphylaxis is needed among health care professionals. By measuring vital signs during a suspected allergic reaction, vasovagal episodes inducing bradycardia and hypotension may be distinguished from anaphylaxis, which generally causes tachycardia and hypotension.

Vasovagal reactions are often very dramatic for the patients, but lack skin symptoms and usually recover spontaneously so that the dentist (or other professional) can carry on with the procedure within minutes. However, the rapid and dramatic presentation may lead to treatment with adrenaline in the acute event and this illustrates how the use of adrenaline cannot always be interpreted as an indicator for anaphylaxis. In fact, in our study, there was no difference in the use of adrenaline between the no allergen group and the other allergen group. The dramatic history is often reiterated by the patient during allergy consultation and may lead to extra care being taken during testing. In this study, the history resulted in 52% of SCPs being performed as titrated provocations, even though all eventually tested negative to LAs.

In patients experiencing in-hospital reactions, a serum tryptase level measurement 1 to 2 hours after the reaction may aid the subsequent allergy investigations. A lack of increase in serum tryptase level compared with a later baseline sample may help confirm a nonallergic mechanism.¹⁸ Evaluating the history during the suspected allergic reaction enhances the possibility for

TABLE II. Clinical characteristics of 164 patients with suspected immediate allergy to LA testing negative to LA on SCP

Characteristic	No allergen*		Other allergen†		P value
Patients, n (%)	147 (90)		17 (10)		
Age (y), median (IQR)	56 (42-65)		57 (53-64)		.988
Sex: female/male	110/37 (75/25)		13/4 (76/24)		.881
Location at reaction time (%)‡					
Dentist	86 (58)		6 (35)		.133
General practice	5 (3)		2 (12)		.142
Specialist's office	24 (16)		1 (6)		.472
Hospital	41 (28)		8 (47)		.090
Symptoms during reaction (%)	No allergen*		Other allergen†		P value
	Yes	No	Yes	No	
Cerebral symptoms	83 (57)	11 (8)	6 (35)	3 (18)	.103
+ Skin symptoms	13 (16)	47 (57)	5 (83)	0 (0)	.001
Skin (%)	49 (33)	58 (40)	16 (94)	0 (0)	<.001
Localized	37 (75)		5 (31)		.003
Generalized	12 (25)		11 (69)		
Treatment (if treated which) (%)	32 (22)	31 (21)	11 (64)	0 (0)	.002
Adrenaline	6 (19)		2 (18)		
Antihistamin	22 (69)		11 (100)		
Steroids	13 (41)		9 (82)		
No specified treatment	2 (1)		0 (0)		

IQR, Interquartile range.

Cerebral symptoms: dizziness, syncope, perioral paresthesia; Localized skin symptoms: localized rash and/or edema; Generalized skin symptoms: systemic rash ± pruritus.

*No allergen, ie, tested negative to LA.

†Other allergen, ie, tested negative to LA but positive to another allergen.

‡Nine patients had more than 1 suspected reaction.

focused testing according to estimated risk. Low-risk patients (no skin symptoms, no comorbidity, and rapid spontaneous recovery) could undergo subcutaneous placebo-controlled full-dose provocation with the culprit LA without previous skin testing. The main purpose of testing in this population is to disprove allergy and convince the patient and health professionals that their reaction was not allergic. In high-risk patients (clear allergy symptoms, severe reactions, and important comorbidity), skin testing should precede a titrated SCP and systematic testing of other allergens with simultaneous exposure such as latex, disinfectants, and antibiotics should be performed.

In this study, skin testing was performed in 20 (12%) patients, considered high risk due to either reaction severity or patient comorbidity. All skin test results were negative, and all patients had subsequent negative SCP. In a recent study of a different cohort of perioperative patients tested with LAs as part of allergy investigations, all patients were systematically tested with SPT, IDT, and SCP. In that study, 2 patients (1.2%) had positive skin test results (patient 1: negative undiluted SPT result, positive IDT result with 0.075% ropivacaine; patient 2: positive SPT result to undiluted bupivacaine, negative IDT result); however, skin test results were deemed false positive because both tolerated the subsequent SCP with the same LA.⁸ This demonstrates why all patients should always undergo SCP with the culprit LA because false-positive skin test results to LAs do occur.¹⁹⁻²¹ It has

been suggested that skin tests are of little diagnostic value in the investigation of allergy to LAs.²² However, in some cases, gradually increasing test invasiveness may be useful to convince patients with a significant element of psychogenic involvement that they tolerate the drug.³

A total of 48 patients (37.5%) were tested with the culprit LA containing adrenaline or another vasoconstrictor. The attending allergologists identified 12 (7%) patients with symptoms (typically tachycardia) attributed to vasoconstrictors during SCP on the basis of lack of skin symptoms and other organ manifestations, and only short duration of tachycardia. Whether SCP should be performed with^{3,23} or without^{17,24} vasoconstrictors is often discussed. A European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology position paper recommends commercially available preparations containing additives with or without vasoconstrictors.²⁵ Testing without vasoconstrictors makes it easier to rule out a reaction to LAs. On the other hand, testing with vasoconstrictors provides the opportunity to assess the symptoms during provocation and reassure the patient that symptoms are transient and harmless. In few cases, it may be necessary to suggest using an alternative vasopressor to adrenaline if symptoms are too uncomfortable to the patient.

Eight patients (5%) were tested only with alternative LA, either because the suspected LA was not available, or because the remitting physician wanted to have a safe alternative for an upcoming procedure. Ideally patients should be tested with the culprit LA because the primary goal is to disprove, and not confirm, allergy. In addition, if the culprit drug is tolerated, all suspicions of cross-reactivity can be ruled out.

LAs are divided into 2 subgroups, ester or amide, on the basis of their chemical composition and metabolism. In Denmark, the ester derivatives are rarely used, which is reflected in this study, because no patients were tested with an ester LA. In several review articles it is argued that cross-reaction is possible within either the ester group or the amide group, but not between groups.^{17,26-28} Most arguments are based on case studies without use of SCP²⁹⁻³¹ or old studies regarding NIR.³² Only a few case studies describe cross-reactivity in immediate-type reactions to LAs using both skin tests and SCP. In 2 studies cross-reactivity was found between the following amide LAs: lidocaine, bupivacaine, mepivacaine,³³ and additionally ropivacaine.³⁴ In the studies SPT results with the undiluted drug and/or IDT 1:100 were positive.

IR differs from NIR in both clinical presentation and immunology. Anaphylaxis, with severe hypotension, tachycardia, and bronchospasm, is the most serious manifestation of IR. In contrast, NIRs to LAs are caused by a contact allergy initiated by skin contact with the allergen causing localized dermatitis (eczematous reactions in the skin surrounding the point of contact), and are never associated with respiratory or circulatory collapse. NIRs to LAs have a higher incidence rate compared with IRs ranging from 2.4% to 4.1%^{35,36} and for lidocaine alone from 0.14% to 5%.³⁶⁻³⁹

It is unknown whether co-occurrence of IR and NIR exists on the basis of the different immunology involved.^{20,40} In our study, 8 patients with suspected NIR to 1 or more LA had a provocation with the culprit drug without developing an IR, but 2 patients developed a localized NIR, both to lidocaine. A recent prospective study including 11 patients with NIR and patch test—confirmed nonimmediate allergy to LAs found that none developed IR to IDT or SCP. However, 3 patients developed a

localized NIR to the SCP similar to our findings. The authors concluded that systemic tolerance to LAs cannot be decided on the basis of a positive patch test result alone. These patients should therefore undergo further testing with IDT and SCP to assess systemic reactivity or tolerance.⁴¹

It would be useful to patients with confirmed NIR to be able to advise on the risks involved in administering LAs by other routes where skin contact is avoided, for example, for an epidural used in labor or spinal anesthesia for cesarean section. Presently the risk is unknown, but it must be remembered that a non-immediate allergy will never result in anaphylaxis, but in theory a systemic contact dermatitis reaction could result.

Further studies of patients with suspected allergic reactions to LAs are needed to determine the incidence of co-occurrence of IR and NIR.

This study is limited by its retrospective design. Patients were not systematically questioned about all symptoms. A prospective study would have provided stronger data regarding symptoms.

Another limitation is that other allergens were not systematically tested in all patients. Patients are exposed to multiple potential allergens in the health care setting, some of which may be less obvious, such as latex and disinfectants, and a study of suspected LA-allergic patients showed that in fact reactions to latex and chlorhexidine were more likely than reactions to LA.³

When planning investigations in suspected LA allergy, like in drug allergy in general, an individual risk assessment is needed to ensure the safest approach for the patient. For suspected LA allergy, this should include the severity of the reaction, comorbidity, level of psychological involvement, and likelihood of an allergic mechanism. Systematic testing with all exposed drugs, including chlorhexidine and other “hidden” allergens such as excipients and latex, should be performed.^{13,42,43} This study shows that immediate allergic reactions to LAs are very rare, regardless of clinical presentation, and therefore most patients suspected of such allergy can be considered to be of low risk. Most patients can therefore be managed using a single full-dose placebo-controlled subcutaneous provocation with the culprit LA without prior skin testing. The incidence of immediate-type cross-reactivity within the LAs is considered extremely low. The incidence of co-occurrence of immediate and nonimmediate reactions is not known and should be the subject of further studies.

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