Original Article

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. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Anaphylaxis; Drug allergy; Immediate hypersensitivity; Local anesthesia*

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 administrated 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 administrated 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 nonimmediate 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 standard[13] 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 performed[15] 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