

No cases of perioperative allergy to local anaesthetics in the Danish Anaesthesia Allergy Centre

A. D. Kvisselgaard, M. Krøigaard, H. F. Mosbech and L. H. Garvey

Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

Correspondence

A. D. Kvisselgaard, Danish Anaesthesia Allergy Centre, Allergy Clinic UA-816GE, Copenhagen University Hospital Gentofte, Kildegårdsvej 28, DK-2900 Hellerup, Denmark
E-mail: akvisselgaard@me.com

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Background: Local anaesthetics (LA) are often suspected as possible causes of allergic reactions. The Danish Anaesthesia Allergy Centre (DAAC) is the national reference centre for investigation of perioperative allergic reactions. The purpose of this study was to investigate the incidence of IgE-mediated immediate type perioperative allergic reactions to LA.

Methods: In the period 2004–2013, a total of 409 patients (244 women/165 men; median age 49 years, range 1–86 years) were investigated in DAAC on suspicion of allergy associated with anaesthesia and surgery. A total of 162 (40%) patients were exposed to one or more LA. Suspected allergy to LA was investigated by prick test, intradermal test and subcutaneous provocation with the suspected drug. Patients with positive skin tests still underwent subcutaneous provocation, as false positive skin tests can occur.

Results: A total of 203 test series with LA were carried out on 162 patients (89 women/73 men; mean age 49 years, range 2–85 years) with the following drugs: Lidocaine $n = 80$ (49%), bupivacaine $n = 82$ (51%), ropivacaine $n = 31$ (19%) and mepivacaine $n = 10$ (6%). All 162 patients had negative subcutaneous provocation for all tested LA (95% CI: 0–1.8%). Investigations revealed another allergen in 52 of 162 patients.

Conclusion: None of the 162 patients with suspected perioperative allergic reactions and exposure to LA reacted on subcutaneous provocation with the relevant LA. Thus, no patients have been diagnosed with allergy to LA in DAAC in the period 2004–2013 and allergy to LA must be considered very rare in this population.

Editorial Comment

Anaesthesiologists frequently suspect local anaesthetics allergic reactions. Lingering suspicion can preclude patients from benefiting from regional anaesthesia. These findings from the Danish Anaesthesia Allergy Centre suggest that this type of allergy is actually very rare, and that suspected allergies to local anaesthetics are usually due to something else.

Allergic reactions during anaesthesia and surgery are rare but can be life threatening. European studies estimate the incidence of

perioperative allergic reactions in the range of 1 : 1480 to 1 : 10 000 anaesthetics.^{1–3} Two American single centre studies reported

incidences of 1 : 677⁴ and 1 : 34 000 anaesthetics,⁵ respectively.

Local Anaesthetics (LA) are commonly used in all branches of the healthcare system, particularly in association with dental procedures, labour and delivery, major and minor surgery and in emergency departments. Exposure to LA is almost inevitable during a lifetime.

Adverse reactions to LA, including allergy, have been estimated to occur in 2.5–10% of cases.⁶ The most frequently reported adverse reactions (ADR) associated with LA are non-allergic such as: Toxicity, vasovagal reactions and the pharmacological effect of added vaso-pressors e.g. adrenaline. For ADR with skin symptoms allergy to other ingredients e.g. preservatives, or allergy to drugs/substances with simultaneous exposure, are more common than allergy to LA.^{7,8}

Immediate type allergic reactions to LA are considered rare by specialists in drug allergy, but for patients and doctors from other specialties, including anaesthesiologists, suspected allergy to LA still present problems. There are only very few studies examining the incidence of perioperative allergic reactions to LA. A French national survey over an 8-year period found six patients (0.33% of the reactions) with allergy to LA.³ Studies of suspected allergic reactions to LA in the general public report an incidence in the range of 0–5%.^{8–15}

Local Anaesthetics are classified based on molecular structure with either an intermediate ester or amid linkage. Traditionally esters are believed to have a higher allergenic potential because they are metabolized to para-amino benzoic acid (PABA) also commonly found in cosmetics.^{16,17} In Denmark ester-LA are infrequently used compared to the newer amides. Previous studies suggested that cross-reactions only occur among ester and not amide LAs.^{10,18, 19} However, recently cases have emerged indicating cross-reactivity among amide derivatives.^{20–24} Generally, investigation protocols differ among studies and many rely only on skin test results, and not subcutaneous provocation which is considered the Gold Standard.

No, or insufficient investigation of a suspected allergic reaction to LA may lead to unfortunate avoidance of LA causing great discomfort²⁵ to the patient and leading to procedures being

performed in general anaesthesia at increased risk to the patient.

The Danish Anaesthesia Allergy Centre (DAAC) is the national reference centre for the investigation of perioperative allergic reactions. Patients have been investigated since 1999; including drug provocation as a standard investigation since 2004.

The purpose of this study was to investigate the incidence of immediate type perioperative allergic reactions to LA in Denmark over the 10-year period 2004–2013.

Materials and methods

This retrospective single centre study involved all patients investigated for perioperative allergic reactions in DAAC in the period January 2004–December 2013 ($n = 409$ patients). In accordance with Danish law, ethical approval was not necessary as all data were collected as part of routine clinical investigations with patients' consent. A total of 162 patients (9 paediatric and 153 adults) exposed to one or more LA were included. A wide range of surgical specialties was represented including patients undergoing caesarean section in spinal anaesthesia. Perioperative allergic symptoms ranged in severity from rash to anaphylactic shock, and in some cases cardiac arrest. The severity of allergic reactions was classified using a previously described classification.²⁶

Investigations were carried out for all drugs patients were exposed to before the allergic reaction using the following criteria: (1) all drugs given intravenously within 1 h of the reaction were tested; (2) all drugs given by other routes e.g. subcutaneously, intramuscularly, epidurally or orally within 2 h of the reaction were tested. Since exposure to chlorhexidine, latex and ethylene oxide were presumed in the perioperative setting all patients were tested with these compounds.

The following diagnostic tests were performed to investigate allergy to LA:

1. *Skin prick test* with suspected undiluted LA on the forearm in duplicate. After 15 min the reaction was read and compared to a negative control with saline. Histamine 10 mg/ml

served as a positive control. A mean diameter of wheal ≥ 3 mm was the positivity criterion.²⁷

2. *Intradermal test* with suspected LA in a 1/10 dilution on the back in duplicate. Since two different criteria for positivity have been used all tests were re-assessed using the following criterion with the highest sensitivity and specificity: Diameter of wheal ≥ 3 mm larger than negative control (saline) at 20 min.²⁷
3. *Subcutaneous provocation* (considered the Gold Standard) was carried out as a single blinded, titrated provocation with an initial placebo control dose.²⁸ A provocation was considered positive on reproduction of symptoms of the original reaction. Patients with positive skin tests still underwent subcutaneous provocation, as false positive skin tests to LA have been described.^{29–31}

The maximum test doses for each drug are summarized in Table 1.

Most paediatric patients underwent the same investigation program. Intradermal testing and subcutaneous provocation was not consistently used on patients < 10 years due to procedure associated pain.

Statistical analysis

Categorical variables were cross-tabulated using Fisher's exact test to examine subgroups. For continuous variables logarithmic transformation with independent-sample *t* test was used. Statistical significance was assumed for $P < 0.05$.

All statistical tests were carried out in IBM® SPSS® Statistics version 23 and descriptive data analysed in Microsoft® Excel® for Mac 2011 version 14.5.4.

Table 1 Maximum doses for allergy testing.

Local anaesthetic	Prick test (undiluted) (%)	Intradermal test (1/10 dilution) (%)	Subcutaneous provocation (mg)
Lidocaine	2	0.2	40
Mepivacaine	1	0.1	40
Bupivacaine	0.25	0.025	5
Ropivacaine	0.75	0.075	75

Results

A total of 203 test series with LA were carried out on 162 patients (89 women/73 men; median age 49 years, range 2–85 years) including nine paediatric patients (median age 15, range 2–17 years). They were tested with the following drugs: Bupivacaine $n = 82$ (51%), lidocaine $n = 80$ (49%), ropivacaine $n = 31$ (19%) and mepivacaine $n = 10$ (6%).

All 162 patients had negative subcutaneous provocations for all tested LA (95% CI: 0–1.8%). Two patients had positive skin tests (Patient 1: positive intradermal test with 0.075% Ropivacaine – negative skin prick test. Patient 2: positive skin prick test to undiluted bupivacaine – negative intradermal test). Both patients tolerated subsequent subcutaneous challenge with the same LA, and skin test results were deemed false positive.

Investigations revealed another allergen in 52 of 162 patients (32%). Table 2 illustrates the differences in clinical characteristics between patients with positive investigations for another allergen and those with negative investigations. There were significantly more males of higher age in the investigation positive group. Patients who were investigation positive had significantly higher serum tryptase at the time of the reaction and higher grade of reaction severity. They also exhibited respiratory and circulatory symptoms more frequently. Patients in both subgroups had a high incidence (85%) of skin symptoms. Approximately half the patients (53%) were under general anaesthesia at the reaction onset and therefore had no cerebral symptoms. Among the awake patients 86% reported no cerebral symptoms, the remaining ($n = 11$) had experienced dizziness or syncope.

For the patients where the investigations revealed another allergen the most frequent were: chlorhexidine $n = 12$, cefuroxime $n = 8$ and patent blue $n = 7$.

Discussion

None of 162 patients with suspected perioperative allergic reactions and exposure to LA reacted on subcutaneous provocation with the relevant LA. Thus, no patients have been diagnosed with allergy to LA in DAAC over the

Table 2 Demographic and clinical characteristics of patients with suspected perioperative allergic reactions.

	Total <i>n</i> (%)	No allergen found <i>n</i> (%)	Another allergen found <i>n</i> (%)	<i>P</i> -value
Number of patients	162	110 (68)	52 (32)	
Age years, mean (range)	49 (2–86)	47 (2–85)	55 (15–86)	0.004*
Gender (F/M)	89 (55)/73 (45)	67 (61)/43 (39)	22 (42)/30 (58)	0.026
Atopy	50 (31)	33 (30)	17 (33)	0.72
ASA classification				
Grade I	74 (46)	53 (48)	21 (40)	0.645
Grade II	72 (44)	45 (41)	27 (52)	
Grade III	15 (9)	11 (10)	4 (8)	
Grade IV	1 (1)	1 (1)	0 (0)	
Severity of reaction				
Grade I	51 (31)	41 (37)	10 (19)	0.0012
Grade II	55 (34)	42 (38)	13 (25)	
Grade III	51 (31)	25 (23)	26 (50)	
Grade IV	5 (3)	2 (2)	3 (6)	
Serum Tryptase				
Reaction - Median (IQR)	6.84 (3.71–19.25)	5.04 (3.24–9.40)	17.7 (5.36–31.4)	< 0.0001*
Control - Median (IQR)	5.06 (3.19–7.20)	4.31 (2.87–6.30)	5.03 (5.07–7.02)	
Reaction symptoms				
Airway	60 (37)	43 (39)	17 (33)	0.488
Breathing	29 (18)	15 (14)	14 (27)	0.048
Circulation	100 (62)	61 (55)	39 (75)	0.024
Skin	137 (85)	93 (85)	44 (85)	0.995
Cerebral status at the reaction				
Under General Anaesthesia (GA)	86 (53)	53 (48)	33 (63)	0.061
Awake (Post-GA)	32 (20)	27 (25)	5 (10)	
Awake (No GA)	44 (27)	30 (27)	14 (27)	
Cerebral symptoms in awake patients				
Dizziness	6 (8)	4 (7)	2 (11)	0.854
Syncope	5 (7)	4 (7)	1 (5)	
No reported symptoms	65 (86)	49 (86)	16 (84)	

Reaction symptoms were defined as: Airway: Laryngeal oedema, angioedema, stridor. Breathing: Bronchospasm, decreased saturation. Circulation: Hypotension, tachycardia, bradycardia. Skin: Urticaria, flushing, unclassified rash, itch. *Independent *t* test after logarithmic transformation. *P*-value < 0.05 significant.

10-year period 2004–2013 and allergy to LA must be considered very rare in this population. There are approximately 400 000 anaesthetics/year in Denmark³² and presuming that 40% of patients are exposed to LA perioperatively a total of 1.6 million patients were exposed over the 10-year study period. Whilst we cannot be sure that all patients with suspected perioperative allergic reactions in the study period have been referred to DAAC, even if we presume a 80% referral rate this would mean no positive reactions to LA in > 1.2 million exposed patients.

Preliminary findings in DAAC from 1999 to 2001 were that six of 54 patients had a positive

intradermal test to a LA. Titrated concentrations from 0.01–1% were used for all drugs, which are higher than concentrations used now (see Table 1). Subcutaneous provocation was not included in the investigations so all six patients were deemed allergic to LA on based skin test results only.³³ With the knowledge from the present study, some of these reactions might have been false positive. A French national survey over an 8-year period found six of 1816 (0.33%) patients with allergy to LA³ but is not specified which type of investigation proved positive. The results were based on data from multiple centres, all following the French guideline, which only includes subcutaneous

provocation if skin tests are negative.²⁶ In our present study two patients had skin tests, which fulfilled the criteria for a positive test, but subsequently both tolerated subcutaneous provocation with the same drug and skin test results were thus false positive.

Intradermal tests have higher sensitivity but lower specificity and are prone to false positive results and this is seen particularly when using undiluted solutions.^{7,9,16,34–36} Generally intradermal test should be performed in a 1 : 10 dilution to avoid irritant reactions as is recommended in a recent European Position Paper on skin test concentrations.³⁷ Subcutaneous provocation is the Gold Standard and should always be included in the investigation of allergy to LA to prevent false positive skin tests, which lead to unnecessary warnings against LA.

This study has only investigated immediate type allergy. Immediate allergy (Type I) and T-cell mediated contact allergy (Type IV) are clinically very different, with different immunology and clinical presentation. Whilst the most serious manifestation of Type I allergy is anaphylaxis, this is not a risk in Type IV allergy where reactions are confined to localized eczematous reactions in the skin and are initiated by skin contact. The reported incidence of Type-IV allergy to LA among patients with a previous reaction ranges from 2.4–4.1%^{38,39} and for lidocaine alone from 0.14–5%.^{39–42} No studies systematically use subcutaneous provocation in the investigation of Type IV LA allergic patients. Therefore, it is not known whether patients with type IV allergies would tolerate LA administered by other routes such as spinal or epidural, where skin contact is avoided. The suspicion of overlap between Type I and type IV allergy frequently leads to inappropriate generalizations, because healthcare workers are usually not able to distinguish between the two types of allergy. Also, the suspicion of cross-reactivity may cause inappropriate avoidances of all types of LA. Further studies are needed to investigate cross-reactivity both within drug types but also between type I and type IV allergy.

For a third of the 162 patients in this study another allergen was found on investigation. The most frequent was chlorhexidine, an allergen that has turned out to be more common in

test series in Denmark compared with other countries.²⁷ Outside the perioperative setting chlorhexidine has also been found to 'mimic' LA allergy.⁸ As a consequence, in DAAC there is focus on all exposures and systematic testing is carried out with chlorhexidine and other 'hidden' allergens such as additives (macrogols, methylcelluloses), ethylene oxide and latex. A systematic individualized investigation protocol is important for correct diagnosis of the causative agent and 'guessing' the culprit in a setting of multiple exposures is not safe.^{28,43,44} In this study, it is not known how frequently LA were thought to be the most likely culprit drug by the referring clinician.

Lastly, it is not known whether the findings in this study could be extrapolated to patients suspected of reactions to LA in other settings such as parturients receiving epidural analgesia or paediatric patients. Presently, in our centre, we do not have a protocol for testing pregnant patients with LA, but the French guidelines on the investigation of perioperative hypersensitivity reactions suggest that subcutaneous provocation with LA is safe in pregnant women, when skin testing is negative.¹⁵

Common differential diagnoses to allergy to LA are vasovagal reactions, toxicity and hyperventilation all with a significant element of cerebral symptoms. If present, these symptoms were missed in half the population in our study who were under GA, but 85% of the awake patients did not report any cerebral symptoms.

In conclusion, allergy to LA during anaesthesia and surgery is very rare. The incidence of allergy to LA during minor procedures performed in LA alone, is not known, and should be investigated prospectively including subcutaneous provocation with the suspected culprit LA.

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