

Risk of True Allergy to Local Anesthetics: 10-Year Experience from an Anesthesia Allergy Clinic in China

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Background: Local anesthetics (LAs) have been widely used throughout the healthcare settings, especially in local anesthesia and pain management. The incidence of allergic reactions to LAs remains uncertain. The danger of allergic reactions to the use of LAs in every day of clinical practice is a matter of great concern. Therefore, it is necessary to investigate the risk of true allergy to LAs.

Methods: This study retrospectively evaluated the medical records of patients who were referred to an anesthesia allergy clinic in China and underwent allergy tests with LAs over a 10-year period from 2009 to 2019. The following information was collected from medical records: demographics of the patients, reasons for referral, clinical features of drug hypersensitivity reaction (DHR), and test results with LAs. Skin tests combined with an in vitro method, basophil activation test (BAT), were used to investigate allergic reactions to LAs.

Results: A group of 109 patients were included in the analysis. The main reason for referral was the presence of a suspected DHR after procedures with LAs (n=68, 62%), the second most common reason for referral was a history of DHR to other drugs and the need to use LAs for upcoming procedures (n=41, 38%). Of the 68 patients with a suspected DHR to LAs, only six cases presented true allergy and showed positive results in skin tests and/or BAT. And all 41 patients who had a history of DHR to other drugs presented negative in all tests.

Conclusion: Risk of true allergy to LAs may be very low. However, patients with a suspected history of DHR to LAs should be considered for allergy tests. Skin tests and BAT may be useful in the investigation and diagnosis of true allergy to LAs in clinical practice.

Keywords: adverse drug reactions, local anesthetics, allergy, skin tests, BAT

Introduction

LAs are commonly used drugs in every day of clinical practice, including dentistry, delivery, and surgery under local anesthesia, which could make the operation safe and painless. It has shown that adverse drug reactions associated with LAs were usually attributed to vasovagal syncope, overdose toxicity, or a reaction to adrenaline.¹ However, the indistinct clinical symptoms after administering LAs are often miscalled as “allergic” by doctors, even if there is no evidence in detailed diagnostic tests.² Patients also usually interpret the side-effects as allergy to LAs and have anxiety about the risk of allergic reactions.

The incidence of true allergy to LAs has not been clearly defined. Despite the frequent use of LAs, IgE-mediated allergic reactions have so far been published only in a few convincing case reports.^{3–5} The incidence of true allergy to LAs is

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considered to be rare by allergists, estimated to be about 1%.^{6–8} A recent study pointed out that the risk of allergic reactions to LAs was commonly overestimated.¹ A Danish national survey over a 10-year period found that none of 162 patients with suspected perioperative hypersensitivity exposed to LAs had been diagnosed with true allergy.⁹

Allergic reactions to LAs during anesthesia and surgery, especially anaphylaxis, can be life-threatening. It is a challenge for doctors to provide appropriate pain management for patients with true allergy to LAs. Inadequate investigation of suspected allergic reactions to LAs may cause anxiety and discomfort to the patient, as well as ongoing concerns of surgeons and anesthesiologist, which may lead to unnecessary delay in surgery or operation without anesthesia, increasing the risk of procedures for patients. Thus, the study aimed to investigate the risk of true allergy to LAs in our anesthesia allergy clinic over a 10-year period from 2009 to 2019.

Materials and Methods

This study retrospectively evaluated all patients who had allergy tests with LAs for any reason over the past 10 years. Cases with incomplete medical records were excluded from the analysis. The study was approved by the Ethics Committee of China–Japan Friendship Hospital. The following information was collected from patients' medical records for each case: demographics of the patients, reasons for referral, the presence of any other allergic diseases, clinical symptoms of drug hypersensitivity reaction (DHR), the history of DHR to LAs and/or other drugs, and test results of suspected and/or requested drugs. The clinical symptoms occurring may involve circulatory symptoms (palpitations, tachycardia, hypotension, shock or cardiac arrest), respiratory symptoms (chest tightness, dyspnea, wheezing, bronchospasm or increased ventilator pressures in intubated patient), cutaneous signs (rash, flushing, erythema, urticaria, or angioedema), and CNS symptoms (anxiety, malaise, sweating, dizziness, somnolence, syncope, or loss of consciousness).

The diagnostic approach was based on the guidelines recommended by the ENDA/EAACI Drug Allergy Interest Group.^{10–13} The diagnostic tests for the allergic reactions to LAs in our anesthesia allergy clinic were performed as follows: skin tests including skin prick test (SPT) and/or intradermal test (IDT), and an *in vitro* method named basophil activation test (BAT). The patients were advised not to take systemically antiallergenic drugs such as antihistamines, antileukotrienes, and steroids for at least 1 week before all the tests

mentioned above. Any drug that induced a positive test result (positive skin tests or BAT) is referred to as the “culprit drug”.

Skin Tests

LAs without vasoconstrictors were used in the skin tests to avoid the appearance of false-positive results.¹⁴ Drugs tested in this study included procaine, lidocaine, bupivacaine, ropivacaine, and articaine. Maximum concentrations of all drugs in the skin tests are shown in Table 1. All tests were performed with positive histamine control (10 mg/mL) and negative saline controls (0.9%). The positive result of the skin tests, suggestive of an IgE-mediated cause, was defined if the diameter of the wheal was at least 3 mm larger than the negative control for SPT, and at least 5 mm larger for IDT. The IDT was performed when SPT was negative.

Basophil Activation Test (BAT)

In all cases of study, patients' blood was collected into K-EDTA tubes. The blood samples were stimulated with the suspected causative drugs within 4 hours. Concentrations used in BAT are listed in Table 1. Experiments were carried out using the Flow CAST kit (Bühlmann Laboratories AG, Switzerland) following the procedures as previously described.¹⁵ The samples were analyzed by flow cytometer. Results were considered positive if activated basophil percentage $\geq 5\%$ and stimulation index (SI=percentage of basophils activated divided by the negative control) ≥ 2 .

Statistics

The statistical analysis was carried out in software SPSS 23.0 and descriptive data was performed in Microsoft Excel 2016.

Results

Demographics and Overview of Test Results

A total of 115 patients who were referred to our anesthesia allergy clinic were evaluated in this study, and 109 patients

Table 1 Maximum Concentrations of LAs in the Skin Tests and BAT

LAs	Original (mg/mL)	SPT (mg/mL)	IDT (mg/mL)	BAT (mg/mL)
Procaine	20	20	2	1
Lidocaine	10	10	1	0.125
Bupivacaine	2.5	2.5	0.25	0.5
Ropivacaine	2	2	0.2	1
Articaine	40	40	4	1

(85 women/24 men; mean age=42 years; range=6–78 years) were included in the analysis. However, six patients did not have complete medical records and were excluded (Figure 1).

Most of the 109 patients were female (n=85, 78%). Forty-eight (44%) out of 109 patients had a history of any other allergic diseases, such as atopy and asthma (Table 2). The main reason for referral was the presence of a suspected DHR after procedures with LAs (n=68, 62%), the second most common reason for referral was a history of DHR to other drugs and the need to use LAs for upcoming procedures (n=41, 38%) (Table 2 and Figure 1). The demographic characteristics of these two group patients are also displayed in Table 2.

Considering the testing procedures, 99 (91%) out of 109 patients had skin tests, and 103 (94%) of these

patients underwent BAT diagnosis (Table 2). In our clinical practice, all patients with a suspected history of DHR to LAs were tested with the suspected LAs, and all patients who had a history of DHR to other drugs were tested with the requested LAs (Tables 3 and 4). Only six out of these 68 patients with a suspected DHR after procedures with LAs presented true allergy to LAs (two patients had positive skin tests – positive BAT; three patients had positive skin tests – negative BAT; one patient had positive BAT but skin tests were not done) (Figure 1 and Table 5). Meanwhile 62 out of these 68 patients presented negative in all tests. Furthermore, all 41 patients who had a history of DHR to other drugs showed negative results for skin tests and BAT (Figure 1).

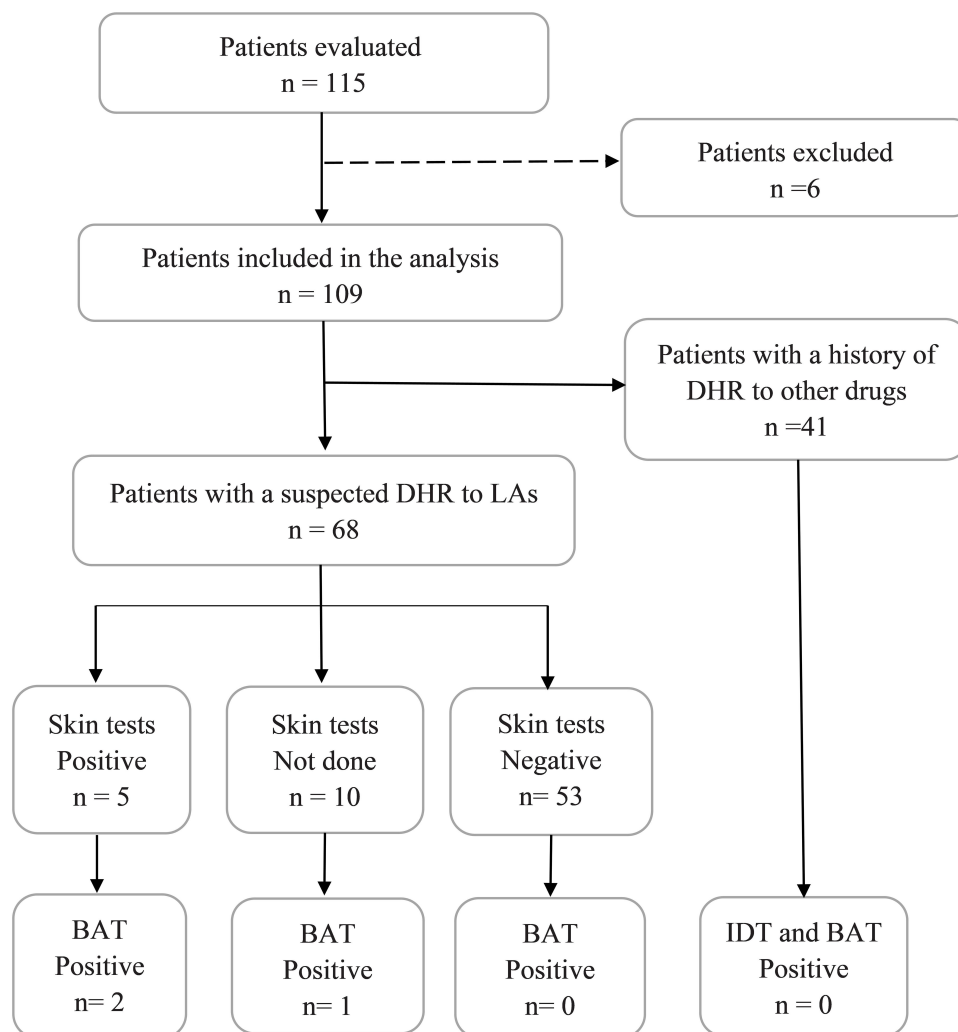


Figure 1 Flowchart of patients evaluated for allergy to LAs.

Abbreviation: n, number of patients.

Table 2 Demographics of the Population Included in the Analysis

Variables	Total, n (%)	Suspected DHR to LAs	History of DHR to Other Drugs
Study population	109	68 (62%)	41 (38%)
Female/male	85 (78%)/24 (22%)	59 (87%)/9 (13%)	26 (63%)/15 (37%)
Age, mean (range)	42 (6–78)	43 (22–78)	40 (6–77)
History of any other allergic diseases	48 (44%)	32 (47%)	16 (39%)
The testing procedures			
Skin tests	99 (91%)	58 (85%)	41 (100%)
BAT	103 (94%)	62 (91%)	41 (100%)

Clinical Characteristics of the Study Population

In this study, 68 patients were exposed to one or more LAs and had a suspected history of DHR to LAs. In most cases,

Table 3 Clinical Characteristics of 68 Patients with a Suspected DHR to LAs

Variables	n (%)
Suspected LAs	68
Procaine	4 (6%)
Articaine	5 (7%)
Lidocaine	31 (46%)
Ropivacaine	2 (3%)
Bupivacaine	1 (1%)
Unknown	25 (37%)
Symptoms of drug reactions	
Cutaneous	22 (32%)
Rash	15 (22%)
Flushing, erythema	4 (6%)
Urticaria or angioedema	3 (4%)
CNS	21 (31%)
Anxiety, malaise, sweating	11 (16%)
Dizziness	4 (6%)
Somnolence, syncope or loss of consciousness	8 (12%)
Circulatory	31 (46%)
Palpitations, tachycardia	15 (22%)
Hypotension	7 (10%)
Shock or cardiac arrest	13 (20%)
Respiratory	19 (28%)
Chest tightness, dyspnea, wheezing	16 (24%)
Bronchospasm	3 (4%)
Others	8 (12%)
Treatment	
Adrenaline	15 (22%)
Others	40 (59%)
No specified treatment	13 (19%)
Outcomes	
The planned procedures were completed	38 (56%)
Postponed for another procedures	25 (37%)
Unknown	5 (7%)

the suspected drug was lidocaine (n=31, 46%), whereas the suspected drug was not known in the 25 cases (37%) (Table 3). The most common clinical symptoms were circulatory (n=31, 46%), followed by cutaneous symptoms (n=22, 32%) and CNS symptoms (n=21, 31%). The exact clinical manifestations of these patients are also shown in Table 3. And 15 (22%) out of 68 patients who showed allergic reactions to LAs were given to treatment with the intravenous administration of adrenaline. In 38 (56%) cases, the planned procedures were completed, and postponed for another session in 25 (37%) cases (Table 3).

Considering the 41 patients who had a previous history of DHR to other drugs, the most common drugs for DHR were general anesthetics (n=25, 61%). In most cases, the requested LAs for upcoming procedures were lidocaine (n=22, 54%). And lidocaine was tested if requested LAs were unknown by their doctors (n=15, 36%) (Table 4).

Clinical Data of Six Patients with Test Positivity to LAs

This study showed that six cases with test positivity to LAs were all women. Four patients had a history of skin reactions after injection of LAs, which were accompanied by respiratory and/or circulatory

Table 4 Overview of 41 Patients with a History of DHR to Other Drugs

Variables	n (%)
History of DHR to other drugs	41
General anesthetics	25 (61%)
Antibiotics	9 (22%)
NSAIDs	2 (5%)
Radiocontrast agent	1 (2%)
Others	4 (10%)
Requested LAs	
Lidocaine	22 (54%)
Ropivacaine	4 (10%)
Unknown (Lidocaine was tested)	15 (36%)

Table 5 Clinical Data of Six Patients with Test Positivity to LAs

No.	Age	Gender	Procedure	Clinical Characteristics	Culprit Drug	Skin Tests	BAT
1	34	F	Surgery	Hypotension, palpitations, shock, angioedema	Ropivacaine	Positive	Positive
2	25	F	Dentistry	Hypotension, palpitation, dizziness, dyspnea, somnolence	Lidocaine	Positive	Negative
3	52	F	Surgery	Hypotension, rash	Ropivacaine	Positive	Negative
4	75	F	Surgery	Tachycardia, malaise, syncope	Lidocaine	Positive	Negative
5	25	F	Dentistry	Dizziness, angioedema	Lidocaine	Positive	Positive
6	29	F	Dentistry	Hypotension, rash	Lidocaine	Not done	Positive

symptoms. However, two patients showed no skin symptoms (Table 5).

According to the skin tests of 99 (91%) patients in this study, five patients had allergic reactions. Of those patients, three cases had a positive IDT with lidocaine, while two cases with ropivacaine. According to the BAT results of 103 (94%) patients in this study, three cases were positive. Furthermore, one patient had a positive BAT but skin tests were not done, the culprit drug was lidocaine (Table 5).

Discussion

A total of 109 patients who underwent tests with LAs in our anesthesia allergy clinic were included in the analysis, only six out of these patients presented true type allergy to LAs. The results showed that risk of true allergy to LAs is very low. A meta-analysis recently showed that true allergy to LAs are extremely rare, it assessed 23 case series involving 2,978 patients between 1950 and 2011, only 29 of these patients presented true allergy to LAs.¹⁶ Although our study was only a summary of the test results in the past decade, it has important potential implications for clinical practice. The DHR during anesthesia and operation, especially anaphylaxis, may be dangerous or even life-threatening to patients and result in lifelong sequelae. Suspected history of DHR to LAs may prompt patients and doctors to reject future LAs injections. If the culprit drug could be investigated and diagnosed promptly and correctly, severe adverse events may be avoided in the follow-up operation. In the current shortage of allergy testing resources in China, it is reasonable to target high-risk patients and those who may have serious complications in the case of allergic reactions during anesthesia procedures. Therefore, despite the low frequency of true allergy to LAs, patients with a suspected history of DHR to LAs should be tested with LAs.

The finding from the Danish Allergy Clinic suggest that adverse drug reactions after administering LAs are usually caused by other nonallergic mechanisms in most cases.¹

These include overdose toxicity with paresthesia and dizziness, vasovagal response manifested as hypotension and syncope, incorrect drug administration, and the influence of adrenaline which is commonly co-administered to increase local duration of action and can lead to palpitations and tachycardia.¹⁷ Each adverse reaction could be confused with allergic reactions to LAs. However, none of these above reactions show skin symptoms. In other words, if adverse reactions to LAs present skin symptoms, such as rash or urticaria, combined with cardiovascular and/or respiratory symptoms, there is a higher risk of identifying allergic mechanisms. Therefore, doctors should immediately identify these systemic reaction symptoms, especially skin symptoms, correctly diagnose and manage patients, and start treatment with the intravenous administration of adrenaline. It is an important differential diagnosis for anesthesiologists to keep in mind and still a major problem in daily clinical practice.

Patients who are allergic to other drugs, especially general anesthesia drugs, are considered high risk groups for allergy to LAs.¹⁸ However, our data showed that skin tests and BAT results were negative for all 41 patients with a history of DHR to other drugs, the results excluded the IgE-mediated allergic reactions. Recently several studies suggested that only a previous history of HDR after exposure to LAs is considered to be at risk of similar or even more severe reactions.^{19,20} A larger cohort study may be needed in the future to determine this potential risk. Guidelines suggested that patients should not be tested for LAs, unless they had a previous history of LAs hypersensitivity.^{11,13} In our daily clinical practice, we noted that some patients who had a previous history of DHR to other drugs were referred to our clinic before a local anesthesia procedure. For high-risk patients or those who may have severe adverse events during anesthesia and operation (such as cardiovascular/cerebrovascular events), they underwent tests with LAs to ensure that requested LAs can be used safely in the future.

The perioperative environment is very complex, and the patient's exposures include anesthetic drugs and other substances. In this case, LAs can present as a potential "hidden allergen", due to lubricating gels and sprays used for endoscopy often containing LAs, but it is rarely recorded on charts.²¹ Furthermore, it has been emphasized that the importance of identifying other simultaneous exposures, which is an important aspect of clinical management in these patients with suspected DHR to LAs.¹⁷ In fact, other drugs and substances commonly used in local anesthesia procedures, such as antibiotics, chlorhexidine, latex, or excipients, are more likely to cause allergic reactions.^{1,22,23} One of the limitations of our research is the lack of evaluation of these agents. Epidemiological studies to assess the incidence and causes of true allergy to LAs have been difficult to conduct, because the other suspected agents are usually unknown and rarely recorded on most medical charts,²⁴ just as in our cases. The lack of these details seriously hinders the correct diagnosis, so it is essential for the close cooperation between allergists and anesthesiologists to conduct highly professional and detailed investigations of suspected allergic reactions.

At present, there are several methods for the diagnosis of drug allergy. However, making the diagnosis is still a complex and challenging issue. Generally, investigation protocols differ among studies and many rely on skin tests, which is considered the Gold Standard, but they cannot be regarded as an absolute diagnosis due to the high rate of false positives.²⁵ And current commercial immunoassays for determining specific IgE levels can only be applied to a restricted number of drugs used during anesthesia.²⁶ Moreover, LAs-specific-IgE assays are not validated, so it is meaningful to develop other reliable diagnostic methods.²⁷ The Basophil activation test (BAT), flow cytometry-assisted technique to quantify the CD63 expression on basophils, may be a new and promising in vitro method for the diagnosis of allergic reactions.^{15,28} The BAT could be used as a supplement to skin tests, especially when skin tests are not available or presented equivocal results, a positive result in BAT may identify the culprit agent.^{28,29} According to the BAT results of 103 patients in this study, three cases were positive. The results suggest that BAT may be useful in the investigation and diagnosis of true allergy to LAs. However, the diagnostic sensitivity of BAT is still unclear, it remains in the experimental stage and has not become a widely used technique in daily clinical practice.²⁷ It is reported that the specificity of BAT is

very high (93–100%), but the sensitivity varies in several studies (63–89.7%) that evaluate BAT in the diagnosis of allergy to neuromuscular blocker (NMBAs).^{30–32} Furthermore, as far as we know, there are no studies to evaluate the use of BAT for routine diagnosis of LAs allergy in China. The investigation of the culprit drug for allergic reactions is still quite difficult, and additional studies need to be done in future to evaluate the sensitivity of BAT.

Conclusions

Over the past 10 years, many patients have been referred to our clinic for allergy tests to find safe LAs that could be used for upcoming surgery. This study showed that risk of true allergy to LAs may be very low. However, patients with a suspected history of DHR to LAs should be considered for allergy tests with LAs. It is necessary to highlight the importance of detailed investigation and complete allergy tests for correct diagnosis and treatment. Skin tests and BAT may be reliable methods for investigation and diagnosis of true allergy to LAs in clinical practice, and this testing procedures could contribute to identifying the extremely rare cases of LAs allergy.

Ethical Approval

The Ethics Committee of China–Japan Friendship Hospital consented to review the anonymous clinical data retrospectively and approved the study (2019-108-K76). Informed consent was not required for a retrospective study. This study was conducted in accordance with the Declaration of Helsinki. All patient data was guaranteed to be confidential, and the researchers were committed to protecting the privacy and personal identity information of patients.

Funding

There is no funding to report.

Disclosure

The authors report that they have no conflicts of interest in this work.

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