

IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective

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Editor's key points

- This is a review of literature on IgE-mediated allergy to local anaesthetics.
- The incidence of IgE-mediated allergy was <1%, based on 2978 referrals reported in 23 case series.
- This review will assist the allergy clinics to design their services, triage referrals, and manage resources.

Local anaesthetic (LA) agents have been routinely used in dentistry, ophthalmology, minor surgery, and obstetrics since the late nineteenth century. Reports relating to adverse reactions and LA allergy have appeared in the published literature for several years. However, the incidence of true, IgE-mediated LA allergy remains uncertain and is presumed to be very low. We critically reviewed the English language literature on suspected LA allergy and its investigation with the aim of estimating the reported prevalence and analysing the role of different tests currently used to identify and confirm LA allergy. Twenty-three case series involving 2978 patients were identified and analysed. Twenty-nine of these patients had true IgE-mediated allergy to LA, thus confirming the reported prevalence of LA allergy in large series to be <1% (0.97%). The protocols used in the investigation of these patients have also been discussed. Evidence from this review confirms the rarity of IgE-mediated allergy to LA and supports an investigation strategy based on using the clinical history to select patients for skin testing and challenge. We believe that such a triage process would alleviate pressures on allergy services without compromising patient safety.

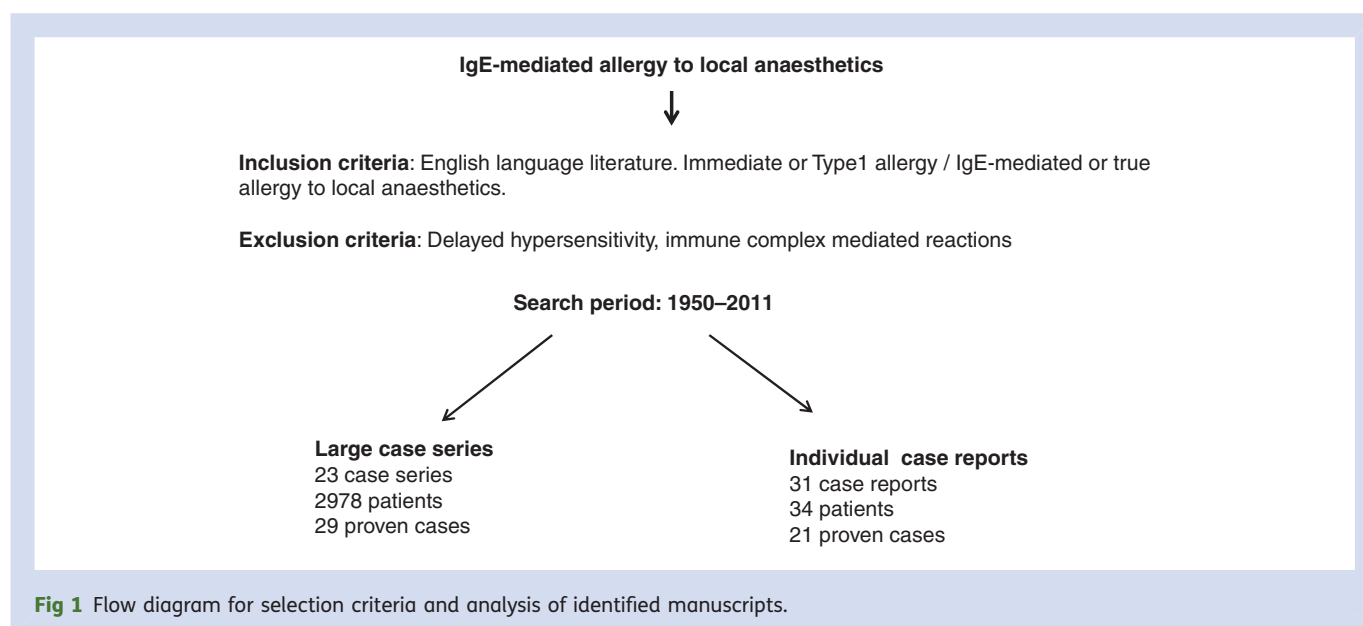
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Local anaesthetics (LAs) have been widely used to prevent and relieve pain in surgical, obstetric, dental, and ophthalmic procedures, since it was first discovered in 1884 by Carl Koller that a solution of cocaine completely desensitized the human cornea.¹ LA agents consist of a lipophilic aromatic ring connected to a hydrophilic amine group and the linking chain is used to classify the agents as ester or amide LA.² LA agents can be administered either topically or by injection (subcutaneously or as a local instillation) and provide complete but temporary analgesia as a result of their interaction with neural voltage-gated sodium channels.³ Adverse reactions have been associated with LA use, since early years. True IgE-mediated allergic reactions are, however, rare and are estimated to be <1% of all reported reactions.^{4–6} The majority of reactions after administration of LA are due to other reasons as summarized in Box 1. Any unusual reaction with LA usage, however, is often loosely attributed to underlying allergy to the drug itself. As a result, these patients are subsequently denied the benefits of LA for future procedures until further immunological evaluation is done.

Box 1 Spectrum of non-IgE mediated reactions to local anaesthetics

- (1) Psychomotor responses
 - Vasovagal attack
 - Hyperventilation and panic attack
 - Endogenous sympathetic stimulation
- (2) Adverse reactions due to other agents administered concomitantly
 - Additives and preservatives
 - Latex allergy
 - Antibiotic allergy
- (3) Responses to procedural trauma
- (4) Delayed hypersensitivity reactions

The British Society of Allergy and Clinical Immunology (BSACI) guidelines on the investigation and management of drug allergy are generic and do not address LA specifically.⁷ Specific protocols for investigating LA allergy have been proposed by groups working in other countries, but these are



time-consuming and do not offer clear guidance on selection of patients for investigation.^{8–13}

Given the rarity of true IgE-mediated reactions to LA and the existing pressures on allergy services within the UK, we have critically reviewed the literature on IgE-mediated allergy to these agents, with a view to ensuring that drug allergy clinics are able to triage referrals and direct their resources at those patients with a history suggestive of IgE-mediated allergy.

Methods and data sources

A MEDLINE search of the English language literature was carried out to identify clinical studies and case reports describing true allergy to LAs. The key search terms used were 'local anaesthetics', 'allergy', and 'true allergy'. The main periods of review were 1990–2011, 1975–1990, and 1950–1975. The types of publications reviewed included large controlled and uncontrolled prospective and retrospective studies, individual case reports, and relevant correspondence. In addition, relevant references were also obtained by scrutinizing the bibliography accompanying chapters on LA allergy from a reputable textbook of allergy.¹⁴ The review of literature was restricted to type 1 or IgE-mediated immediate hypersensitivity and the articles referring to delayed type hypersensitivity were excluded from consideration (Fig. 1).

In addition, drug analysis print (DAP) data derived from the UK yellow card reporting scheme for lidocaine, bupivacaine, tetracaine, articaine, levobupivacaine, procaine, ropivacaine, prilocaine, and benzocaine were obtained from the Medicines and Healthcare Products Regulatory Agency (MHRA) website for the period between 1963 and 2010 [<http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/Yellow>

[Carddata/Druganalysisprints/index.htm](http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/YellowCarddata/Druganalysisprints/index.htm) (accessed on 5 March 2012)].

Results

Twenty-three case series involving 2978 patients with suspected LA allergy and 31 individual case reports were identified that described evaluation and testing for true allergy to LAs. These have been summarized in Table 1 (large case series) and Supplementary Table S1 (individual case reports), respectively. Individual case reports were not included in the calculations for the incidence of true allergy. Similarly, data from the UK yellow card reporting system (DAP data: Supplementary Table S2), briefly discussed below, was excluded from the calculations.

Case series

True IgE-mediated allergy to an LA agent was proven in 29 patients out of a total of 2978 patients screened in the larger series. This makes the reported prevalence of LA allergy in the literature <1% (0.97%).

In 75% (22/29) of these cases, this was clearly documented to an amide agent (Table 2). The predominance of amide agents as allergenic triggers in contrast to esters probably reflects the current practice of preferential use of amide agents for local anaesthesia.

Individual case reports

Twenty-one patients of the 34 individual cases (61.7%) were reported to have true IgE-mediated allergy. Of these 21 patients, 16 were shown to be allergic to an amide agent. Variable protocols have been used for the investigation of these patients in different centres. The protocols used in the case reports have often been tailored to suit the individual clinical situation. Most investigators have used a combination of skin tests and challenges as detailed below.

Table 1 Large studies and case series. NC, not clear; ND, not done

Study	Ref no.	Number of patients	Patient selection and relevant clinical history	Positive tests		Challenge	Conclusion
				Skin prick test	Intra-dermal test		
Tomoyasu and colleagues	47	20	Retrospective analysis of patients with histories of adverse reactions to LA between April 2004 and March 2009	ND	3/17	0/13	One out of the 20 patients screened was proven to have immediate hypersensitivity to mepivacaine. Two patients had false-positive intra-dermal tests
McClimon and colleagues	16	178	Retrospective chart analysis of patients undergoing LA skin testing over a 16 yr period between 1992 and 2008	1/178	4/178	3/173	Out of the five patients with positive skin tests, one had equivocal local reaction on open challenge, three had negative challenges and one did not undergo challenge. Negative predictive value of skin tests was found to be 97%
Harboe and colleagues	15	135	Retrospective analysis of patients referred to allergy clinic for evaluation of suspected LA allergy between 1995 and 2006	0/135	0/135	1/135	One patient identified with immediate hypersensitivity to LA after positive subcutaneous challenge with neat solution. Ten patients were found to have IgE-mediated hypersensitivity to an agent other than LA. A suitable LA for future use was identified for all patients
Fuzier and colleagues	18	286	Retrospective analysis of all spontaneous reports submitted to the French Pharmacovigilance (PV) centre between 1995 and 2006. 286 reports with suspected LA allergy identified and analysed. Reports from GERAP database (study group of peri-anaesthetic allergy reactions) between 1985 and 2006 were also analysed	1/286	1/286	3/286	Three patients out of 286 reports from the French pharmacovigilance database had true immediate reaction to LA. Additional eight cases of immediate hypersensitivity were identified from the GERAP database over a 20 yr period
Wohrl and colleagues	17	36	Retrospective analysis of 291 patients who presented to allergy clinic with a history of drug allergy. 36 patients had a history of LA allergy	2/36	2/36	2/36	Two confirmed positive reactions with provocative challenge, alternative agents found in 34 patients
Jacobsen and colleagues	48	48	Patients referred to allergy clinic with reactions to LA	3/48	3/48	2/48	Two were true positive with type I reactions, 1 patient had delayed hypersensitivity. In all cases, a safe alternative agent was successfully found after subcutaneous challenge
Amsler and colleagues	45	199	Detailed questionnaire to dermatologists analysis of direct re-challenge in 199 cases	NC	NC	1/199	One case of true hypersensitivity, nine vasovagal, and one psychogenic
Berkun and colleagues	37	236	Patients referred to allergy clinic for evaluation of LA hypersensitivity. 142/236 h/o previous immediate reactions	0/236	0/236	1/236	Study used alternative agent for testing and supports safety of incremental challenge. In the one positive case, another safe LA was found
Baluga and colleagues	49	25	5018 patients who received LA for dental treatment were screened 25 patients with adverse reactions in 1st hour were assessed	0/25	0/25	0/25	Overall incidence of adverse reaction 0.5%, no immediate allergic reaction, 22/25 psychogenic/vasovagal, 1 defective technique, 2/25 delayed reaction

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Table 1 Continued

Study	Ref no.	Number of patients	Patient selection and relevant clinical history	Positive tests		Challenge	Conclusion
				Skin prick test	Intra-dermal test		
Macy	41	252	Reviewed records of patients investigated for LA allergy with lidocaine containing methylparaben	3/252	1/252	0/252	Three positives reacted to methylparaben, but not to pure LA
Astarita and colleagues	50	198	72/198 patients had previous h/o adverse reactions to LA	0/198	0/198	0/198	No patient had positive tests for immediate hypersensitivity. Two patients had positive patch test. In a 3 yr follow-up after investigation, 1017 uneventful mepivacaine administrations were recorded
Nettis and colleagues	10	105	Total 432 patients tested using incremental challenge. 105 patients had a previous history of adverse reactions to LA	0/105	0/105	0/105	Incremental tests plays major diagnostic role. No positive tests in group with h/o previous reactions
Cetinkaya	51	157	157 patients with asthma and atopy tested. 125 had previous LA. 3/125 reported adverse reaction	0/157	0/157	0/157	Incidence of true allergy to LAs not higher among atopic/asthmatic children
Hein and colleagues	52	32	Study to examine the diagnostic value of systemic provocative tests. Total 56 patients studied with reactions to antibiotics, NSAIDs, and LA	0/32	NC	1/32	Non-specific symptoms even in the placebo group, systemic provocation tests should be done with placebo for validation. Incremental challenge tests can be safely used to investigate adverse reactions
Troise and colleagues	53	386	Patients with risk for adverse reaction to LA tested with amide agent without epinephrine and preservative	13/386	3/386	0/13	Only patients with positive SPT had had subsequent challenge. Three patients who also had positive intra-dermal test were successfully challenged with alternative agents
Wildsmith and colleagues	54	25	Previous history of acute event with exposure to LA	NC	NC	1/25	One true allergy to the amide group
Fisher and Bowey	55	208	Retrospective analysis of records of patients referred with h/o allergy to local anaesthesia over a 20 yr period	ND	4/208	1/202	Four patients with immediate and four with delayed hypersensitivity and 39 with possible reactions to additives
Gall and colleagues	56	177	Patients with at least one episode of adverse reaction to LA	0/177	0/177	3/177	One proven delayed type allergic reaction, two immediate reactions, but not IgE-mediated (no specific IgE detected)
Wasserfallen and Frei	11	28	Patients with a previous history of adverse reactions to LA were evaluated	4/28	10/28	0/28	All patients tolerated challenge. 19 patients were re-exposed with LA 16–50 months after evaluation—no reactions
Chandler and colleagues	38	59	Retrospective review of all referrals for LA allergy between 1965 and 1985	0/59	ND	0/54	No positive tests to skin prick. Three patients had uneventful, inadvertent re-exposure to LA before testing two patients requiring LA for arrhythmias were successfully given full i.v. dose after negative skin test
Fisher and Graham	36	27	Progressive challenge used to evaluate 27 patients with a history of adverse reaction to LA	ND	1/27	0/26	True allergy in one patient; however, method did not exclude reactions to additives and preservatives to LA

Continued

Table 1 Continued

Study	Ref no.	Number of patients	Patient selection and relevant clinical history	Positive tests		Challenge	Conclusion
				Skin prick test	Intra-dermal test		
deShazo and Nelson	39	90	Referrals for previous immediate hypersensitivity reactions	0/90	10/90 (neat) 0/90 (diluted)	0/90	Supports usefulness of skin test and progressive challenge in the management of suspected LA allergy
Incaudo and colleagues	40	71	Retrospective review of patients with suspected LA allergy	3/59	5/59	0/50	All patients had successful challenge with alternative agents. Three patients tolerated a challenge with the LA that they tested positive on SPT

Table 2 Details of amide and ester LA agents used in large series. NC, not clear; ND, not done

Study	Number of patients	LA agent used for tests		Patients with positive skin tests	LA agent tested positive		Additional comments
		Amide	Ester		Amide	Ester	
Tomoyasu and colleagues	17	17	0	1	1	0	One patient was true positive, two had false-positive reactions
McClimon and colleagues	178 (227 skin tests)	199	28	4	4	0	Some patients were tested to more than one LA
Harboe and colleagues	135	135	0	1	1	0	
Fuzier and colleagues	286	286	0	3	3	0	
Wohrl and colleagues	36	36	0	2	2	0	
Jacobsen and colleagues	48	48	0	2	2	0	
Amsler and colleagues	199	199	0	1	1	0	
Berkun and colleagues	236	236	0	1	1	0	
Baluga and colleagues	25	NC	NC	0	0	0	
Macy	252 (290 skin tests)	287	3	3	3	0	Some patients were tested with and without methylparaben. One patient was also tested with three ester LAs. No true positives
Astarita and colleagues	198	198	0	0	0	0	
Nettis and colleagues	105	105	0	0	0	0	
Cetinkaya	157	157	0	0	0	0	
Hein and colleagues	32	32	0	1	1	0	
Troise and colleagues	386	386	0	3	3	0	
Wildsmith and colleagues	25	NC	NC	NC	NC	NC	One true allergy to the amide group on challenge
Fisher and Bowey	208	NC	NC	4	NC	NC	Four patients with immediate hypersensitivity
Gall and colleagues	177 (197 skin tests)	186	11	2	2	0	
Wasserfallen and Frei	28 (112 skin tests)	84	28	14	9	5	All patients were tested with three amide and one ester LA using skin prick and intra-dermal test. No true positive on challenge
Chandler and colleagues	59	59	0	0	0	0	
Fisher and Graham	27	NC	NC	1	NC	NC	Positive IDT in one patient. LA agent not clear
deShazo and Nelson	90	90	0	0	0	0	
Incaudo and colleagues	71 (117 skin tests)	118	59	5 (12 tests)	8	4	All patients tested with two amide LAs and 1 ester LA by prick test and IDT. Three patients tolerated subsequent challenge with same LA. Two patients with true allergy—agent not clear

Skin prick tests

In the 23 large series, 2487 out of 2978 patients (83.5%) were tested using this method. Thirty (1.2%) had positive results. Most of the patients were tested to more than one agent, including the suspect agent, wherever known. This test was used in combination with the clinical history to identify a suitable agent for subcutaneous challenge. Many authors have used undiluted LA for skin prick tests (SPTs),^{10–12 15 16} although some have preferred to use dilutions.^{13 17}

Intra-dermal tests

Intra-dermal tests have been used variably, either with or instead of SPTs in the initial investigation of these patients. Of 2978 patients, 2648 (89%) had intra-dermal testing. Thirty-seven of these were positive (1.4%) when using 1:10 or greater dilutions of LA. Neat preparations of LA were not commonly used for intra-dermal testing.

Subcutaneous challenge

Of the total 2978 patients, 2560 patients (86%) investigated for LA allergy in the case series had subcutaneous challenges. Positive challenge tests were reported in 19 patients (0.74%). In most cases, this procedure has been used to demonstrate tolerance to an alternative agent rather than confirm allergy.

DAP data

Data from the MHRA regarding reports of possible immune-mediated reactions to lidocaine, bupivacaine, tetracaine, articaine, levobupivacaine, procaine, ropivacaine, prilocaine, and benzocaine are shown in Supplementary Table S2. The yellow card reporting system that is used to collect these data allows registration of all suspected cases of adverse reactions after LA administration. These data are not clearly designed to differentiate between different types of reactions or demonstrate that the aetiology of these cases was proven by investigations. We have therefore not used these data for the purpose of calculations.

Discussion

True IgE-mediated allergy to LAs is rare and previously reported to be <1%.^{4–6} In this review, the analysis of published series and large studies of suspected cases of LA allergy in the English literature between 1952 and 2011 has confirmed this finding. The calculated incidence of reported cases of true IgE-mediated allergy to LA was found to be 0.97%. Individual case reports describing patients with documented and proven allergy to LA preparations were noted and recorded separately, but not included in the calculation of the incidence with a view to avoiding bias.

Review of the DAPs between 1963 and 2010 from the 'yellow card' reporting scheme used in the UK showed one recorded case of type 1 hypersensitivity to tetracaine when single active constituent products were analysed. Multiple

active constituent groups showed five additional cases with type 1 reactions. This scheme records all reported adverse events and includes immune-mediated reactions, anaphylactoid reactions, and also reactions to preservatives and additives within the product. A similar analysis reported by a French group of 210017 adverse reactions registered in the French Pharmacovigilance database over a 12 yr period between 1995 and 2006 identified 286 reports of suspected LA allergy.¹⁸ Seven of these cases were selected on the basis of the history for further investigation and immediate allergic reactions were found in only three cases. Additionally, eight patients with immediate reactions were also identified from the GERAP (a French study group of peri-anaesthetic anaphylactoid reactions) database over a period of more than 20 yr (1985–2006). The true-positive cases described in individual case reports or identified by nation-wide surveillance schemes, considered in the context of the total number of patients receiving LA agents on a daily basis, support the safety profile of these agents and the low incidence of IgE-mediated reactions to them.

Adverse reactions to LA agents

LA agents are broadly divided into two main groups depending on their chemical structure:

- amino-ester compounds: benzocaine, procaine, and butacaine;
- amide compounds: lidocaine, bupivacaine, and prilocaine.

Theoretically, adverse reactions to LAs may occur as any one of the well-recognized Gell and Coombs hypersensitivity responses: namely, IgE-mediated, immune-complex disease, and delayed type hypersensitivity. Delayed hypersensitivity to LA as demonstrated by a positive patch test is well documented in the literature.^{19–21} Some reports also suggest an immune complex mediated aetiology to LA reactions where symptoms are associated with reduced complement levels.^{22 23} In the early years of anaesthetic use, there were reports of deaths attributed directly to the use of the ester group of LAs, especially cocaine hydrochloride and procaine hydrochloride.^{24 25} However, it is not clear if these represent pharmacological reactions or true allergy.

Adverse reactions to ester compounds, especially contact dermatitis, are more commonly reported in the literature; however, there have also been sporadic reports of IgE-mediated reaction to ester agents.^{26 27} Amino-ester compounds are derivatives of para-amino benzoic acid (PABA), a common additive in lotions, cosmetics, and sunscreens. It is hypothesized that previous exposure to such PABA-containing products can potentially sensitize a susceptible individual to amino-ester based LA agents.²⁸ Methylparaben, a preservative agent used in both ester and amide LA preparations, is also metabolized to PABA. Allergy to methylparaben may account for a significant proportion of the adverse reactions to LA.²⁹ It has therefore been recommended

that patients be also evaluated for paraben allergy during investigation.

Amide compounds are increasingly preferred in clinical practice as reactions to these agents are considered to be less common than the amino-ester group. There have, however, been reports of patients with true allergy to amides and documented cross-reactivity within the amide group.^{30–32} This has also been described in earlier studies of patients with contact dermatitis and delayed hypersensitivity based on patch test results.^{28 33}

Investigation of suspected LA allergy

Allergic reactions to LA agents have been postulated to be mediated via a hapten/hapten-carrier protein complex.³⁴ Investigations to find specific IgE to LA agents are still experimental.³⁵ This makes it difficult to have a reliable serum test to identify patients with sensitivity to LAs. Although serial measurements of serum mast cell tryptase concentrations immediately after a suspected reaction to the anaesthetic agent are recommended in the recently published guidelines by the BSACI,⁷ tryptase levels are often lacking in the published literature on LA allergy.

Evaluation of patients with a history of LA allergy has thus relied on careful and detailed history followed by direct SPTs using the suspect agent itself.^{8 9} Schatz⁹ has described protocols for both skin testing and subcutaneous incremental challenge in detail in 1984. On review of the literature, it has been interesting to note that there is a significant variability among clinicians with the protocols used for investigations. Most investigators have used a combination of skin tests and challenges to confirm diagnosis and find alternative agents, and protocols have often been tailored to suit individual clinical situations. The majority of authors have used or recommended vasoconstrictor-free preparations with or without preservatives,^{8–10 12 13 16 36} although a few have preferred to use preparations that contain these reagents on the basis that these are the products that are being used clinically in their local practice with or without preservatives.^{15 37}

Skin prick tests

SPTs have been used as the initial investigation in the assessment of patients with suspected LA allergy. The number of agents to which the patients were tested, depended upon the available history. It is not uncommon for a patient to be tested to a range of LA from both amide and ester groups, including the suspect agent. SPTs are relatively easy and safe to perform, and in conjunction with the clinical history often helps to determine the most suitable LA for subsequent challenge testing. McClimon and colleagues,¹⁶ in their review of 178 patients undergoing 227 skin tests, reported the negative predictive value of skin tests for LA allergy to be 97%.

Intra-dermal tests

Intra-dermal tests have been used either with or instead of SPTs. However, in addition to being a painful procedure for

the patients, they are also associated with a high false-positive rate (8–15%).³⁸ deShazo and Nelson noted a high degree of false-positive reactions (10/90 patients) while using the neat solution for intra-dermal testing as opposed to a 1:10 dilution (0/90 patients).³⁹ Four of these patients were then successfully challenged with the same agent without any reactions. The false-positive tests were presumed to be due to a primary irritant effect. Similarly, Incaudo and colleagues⁴⁰ also reported five positive reactions after intra-dermal testing, three of these patients were challenged with the same agent and had no reactions. Analysis of the published data within our review also showed a higher positive rate with intra-dermal testing (37/2648—1.4%) when compared with positive reactions as determined by challenge tests (19/2560—0.74%). The combination of a painful procedure with a high false-positive rate argues against the routine use of this test in the investigation of patients with suspected LA allergy.

Subcutaneous challenge tests

Subcutaneous challenges are considered to be the gold standard for confirmation of true IgE-mediated allergy to LA. However, challenge tests or drug provocation tests as a part of allergy investigations are generally controversial, especially if the suspect agent is being used for the test. One of the main arguments against drug provocation tests is the ethical issue of exposing a well patient to a dose of the suspect agent when they are otherwise normal (at the time of testing). Drug provocation tests should therefore be performed ideally in a hospital setting with easy access to emergency management, if required. This results in a substantial increase in the overall cost of investigation, which has also been the subject of discussion. Despite this, it is often essential to subject patients with suspected LA allergy to challenge testing in order to provide a safe alternative agent for future use. Protocols for challenge tests have been described in detail in earlier papers.^{9 40} These have been subsequently modified by investigators to suit individual needs.^{38 41} Provocative challenge testing as described by Chandler and colleagues³⁸ has its role in certain clinical situations, particularly in pregnant women presenting late to the obstetrician with a history of allergy to LAs, as used by other groups.^{42–44} It provides a useful method to identify a safe alternative for the individual patient. In the absence of a history clearly suggestive of type I allergy, direct re-challenge may be considered a safe and cheap alternative as opposed to embarking on lengthy and time-consuming investigations.⁴⁵

Subcutaneous challenges, however, are not without potential risk and it is recommended that the clinician estimates the risk-benefits for each individual case before initiating the challenge. It has been shown in previous studies that shorter challenge protocols can be safely used for the investigation of LA allergy.^{38 41} It is possible that selected patients with a history of a reaction to LA and negative SPTs may safely be tested with an alternative LA using a

much shorter protocol or even just a single-dose subcutaneous challenge. This is only possible with LA agents because it has been repeatedly shown by several investigators that true IgE-mediated reactions to LA are very rare. This approach may help to considerably shorten the evaluation time and also provide a safe alternative for future use.

Cross-reactivity between LAs

The primary objective of the assessment of suspected LA allergy in the drug allergy clinic is to identify an agent that can be safely used in the future. It is therefore important to consider the possibility of cross-reactivity between different agents. Amide compounds are increasingly preferred in clinical practice as reactions to these agents are considered to be less common than the amino-ester group. There are reports of patients with true allergy to amides and documented cross-reactivity within the amide group.^{18 30–32 35} The importance of considering cross-reactivity and skin testing with several LA in order to identify a safe one has recently been highlighted by Fuzier and colleagues.¹⁸ Cross-reactivity between the amide and ester groups has only been reported rarely, and when it has been reported may be attributed to paraben allergy in preservative containing amide preparations or co-sensitization.^{13 43 46}

Implications for UK practice

The BSACI guidelines on the investigation and management of drug allergy clearly stipulate that all suspected cases must be referred to specialist allergy clinics for further investigation.⁷ In the light of this review reiterating the rarity of IgE-mediated allergy to LA and given the current pressures experienced by the allergy services within the UK, we propose that only carefully selected patients with a good clinical history are referred for further investigation to the allergy services. Previously published algorithms are helpful in this regard.^{9 13}

Conclusion

This review of currently available data on adverse reactions to LA has reiterated the overall safety of these agents in clinical practice. Adverse reactions to LA are more often than not secondary to other causes rather than true IgE-mediated allergy.

The investigation of patients with suspected allergy to LA should begin with a detailed history which should then determine whether skin testing and challenge is warranted. The evidence from this review shows that incremental challenge in patients with negative skin tests invariably demonstrates that the patient is tolerant of the relevant LA. In the light of these data, we therefore propose a single subcutaneous injection of the particular LA after negative skin tests is likely to be an adequate substitute for incremental challenge in this group of patients. For those patients with positive skin tests (skin prick, intra-dermal, or both), we suggest that skin testing and challenge with an unrelated LA be used to predict future safety.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

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