

INTRADERMAL TESTING ON PATIENTS WITH PUTATIVE ALLERGIC REACTIONS TO LOCAL ANAESTHETICS – ANALYSIS OF 611 CASES

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SUMMARY

Background. Although allergic reactions to local anaesthetics (LAs) of the amide type are relatively rare, many patients and practitioners label any adverse reaction after administration of an LA as 'allergic'.

Objective. The aim of this study was to evaluate the reliability of intradermal testing (IDT) of patients with a history of adverse reactions to LA, and to rule out a possible allergy so an alternative LA, unlikely to cause any reaction, could be selected.

Methods. IDT was done on 611 patients referred to the author for assessment of LA allergy.

Results. Positive skin reactions were found in 15 patients (2.5%). All responded favourably when a different amide LA was prescribed.

Conclusion. These results indicate that IDT is safe and can be used to identify an LA that patients with a prior history of adverse reactions can tolerate.

Local anaesthetics (LA) (except cocaine) are small organic molecules, with molecular weights of less than 300 Dalton. They are too small to be antigenic, but sufficiently foreign to bind as a hapten to tissue or plasma proteins to form an antigen which initiates sensitisation in susceptible individuals.

Allergic reactions to LA agents of the amide type are relatively rare. Although the incidence is not known, it has been widely quoted that less than 1% of all reactions to LA are allergic.¹⁻⁶ Many patients and some clinicians immediately declare any adverse reactions that occur after an LA injection an allergy. Unfortunately, however, many patients who have experienced these reactions never have diagnostic tests to determine the cause of the reaction. This may lead to reluctance on the part of the dental practitioner to administer LA and to provide dental service for these individuals. Many of these patients avoid dental care or undergo general anaesthesia for their regular dental visits.⁷

Testing for LA allergy includes *in vivo* tests such as prick, scratch and patch testing, intradermal injection and challenge with increasing doses. *In vitro* tests like the lymphocyte transformation test and the leucocyte histamine test have the advantage that the patient is not exposed to the suspected allergen, but they are not foolproof. These tests may miss allergy due to hapten formation.² Radio-allergosorbent tests (RAST) used for the detection of IgE antibodies to LA are not available.⁸

In Malamed's *Handbook of Local Anesthesia*⁹ the author states that no form of allergy testing is 100% reliable. The primary mode of assessing a patient for LA allergy is intracutaneous injections. He claims that this method is 100 times more sensitive than other forms of cuta-

neous testing. Skin testing can be used to differentiate an immunological reaction to LA from an autonomic or toxic adverse effect.¹⁰ Burr¹¹ also made the observation that skin tests are useful in showing the relative importance of different allergens.

De Shazo and Nelson¹² reported on 90 patients referred to their allergy clinic. Intradermal testing (IDT) was performed with full-strength and 1:100 dilutions of lidocaine and other LAs. They concluded that IDT is a useful approach in the management of alleged LA hypersensitivity. In 1984 Fisher¹³ published his detailed methodology, interpretation and rationale for IDT. He used freshly prepared LA solutions and injected 0.2 ml of solution, containing 0.2 µg of LA. Over an 11-year period 268 patients were tested. He claimed that IDT should be the minimum investigation after anaphylactoid reactions to LA. In a follow-up publication,¹⁴ he and his co-author reported on their findings after performing IDT in 208 patients. They found that 197 (95%) were not allergic to LA. They concluded that a history of LA allergy is unlikely to be genuine and that LA allergy is rare.

A comparison of patch testing with prick and IDT was published.¹⁵ Out of 104 patients patch-tested for the diagnosis of allergic contact dermatitis, 63 demonstrated positive reactions to the substances of the caine mix (benzocaine, procaine, amethocaine and procaine). On prick testing there were no positive results. IDT with procaine yielded positive results in 9 patients, and with butanilcaine there were positive results in 3 patients. They concluded that there was a very low risk of an anaphylactic reaction after the intradermal injection of LA (1:10 dilution). In an investigation to compare intradermal and patch testing of patients with nickel allergy, the results indicated an increased accuracy of intradermal testing over patch testing; this was also found in tuberculin testing.¹⁶

When the reactions to scratch and IDT with a variety of LAs were examined in 90 patients and 45 controls,¹⁷ it was found that scratch testing did not appear to discriminate between the two groups. However, a significantly greater number of patients than controls produced a positive IDT. Gall, Kauman and Kalveram¹⁸ in their analysis of 19 cases of adverse reactions to LA, also utilised prick tests and IDT. All these were negative. Only 3 patients reacted positively after subcutaneous challenge with the causative drug.

In an investigation designed to evaluate the long-term usefulness of skin and incremental challenge in patients with histories of adverse reactions to LA, Wasserfallen and Frei¹⁹ assessed 28 patients over a period of 3 years. They reported that adverse reactions to LA are in most cases not allergic in nature. However, evaluation protocols, although time consuming, are effective in selecting an agent to which the patient is tolerant. In a report on the management of 386 patients at risk for adverse reactions to local anaesthetics, the authors used both IDT and progressive subcutaneous challenge to select a safe LA. They found that skin tests and subcutaneous challenge are safe and sufficiently reliable to identify LAs which patients could tol-

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erate.²⁰ In another study to evaluate the incremental challenge test in the diagnosis of adverse reactions to LA, the authors concluded that they were able, in nearly all cases, to select LAs that were safe and reliable.²¹ The objective of Wildsmith and co-workers²² investigation was to identify the true nature of acute reactions in 25 patients initially diagnosed as being allergic to LA. Intradermal injections of saline and different concentrations of preservative-free lidocaine were used. All the reactions could be classified under three headings: an immunological reaction to a different antigen; a manifestation of anxiety; or an iatrogenic problem. The group concluded that all adverse reactions to LA must be assessed carefully and specialist referral may be appropriate. This conclusion is in accordance with the views of other authors²²⁻²⁴ who stressed the importance of thorough investigation of all cases of putative allergy. In a monograph on LAs De Jongh¹ states that the consensus view relegates IDT as useful primarily as a screen. A negative test is not an absolute guarantee of immunological unresponsiveness, but it does rule out catastrophic anaphylactic reactions. He concluded that IDT is best left to the specialist.

OBJECTIVE

The aim of this study was to determine the frequency of positive IDT in patients with a reported history of LA allergy and whether negative reactions may indicate which LA could be used for routine dental treatment. The hypothesis tested is that IDT in patients with reported adverse reactions to LA is of value in identifying those agents to which the patient is unresponsive and which can be used safely in the dental treatment in these individuals.

MATERIALS AND METHODS

From 1 January 1984 all patients referred to the author for the investigation of putative allergic reactions were subjected to IDT.

The following protocol based on the methodology published by Fisher was used.^{12,25} A detailed history of the 'allergic event' was obtained from the patient. Patients were specifically asked if the services of a physician, paramedic or hospital had been required. This information may help to ascertain whether the event was allergic, vasovagal, adrenaline-induced or the result of another adverse reaction to the LA. A clinical history, designed to identify drugs that could modify the patient's response, was acquired. Patients were also questioned about the existence of other allergies. A blood sample for a total serum IgE was also obtained from every patient.

All IDT was done at a venue where resuscitation facilities are available. IDT includes a buffered normal saline control to ensure that one is not dealing with a demographic subject. The antigen (hapten) is diluted in buffered normal saline immediately prior to testing. The volume injected is 0.05 ml containing 2 mcg of one of the following LAs: lidocaine, mepivacaine and prilocaine.

The intradermal response was monitored and measured after a 10-minute period. A positive response to any LA was recorded when the wheal and flare was 2 mm or more than that of the saline control. A report was sent to the referring practitioner with a recommendation on which LA to use in future. Practitioners were requested to report back on the response of the patient to the recommended LA. In all cases where a positive response was found, the author administered an amide LA different from the one that had caused a positive response.

Dental practitioners (DPs) are bad correspondents. It

was decided to request by way of a questionnaire an evaluation of the usefulness of the IDT procedures, upon which the recommendations on which LAs to use in future were based. In the same questionnaire DPs were also requested to indicate how many units of LA are used per week. The purpose was to calculate the approximate number of LA units per working day used by DPs in the city of Pretoria, South Africa.

RESULTS

Six hundred and eleven patients were referred to the clinic in the 17-year period. Their mean age (standard deviation (SD)) was 38.3 (14.7) years and the range 6-78 years. The gender distribution was: 486 (79.5%) female and 125 (20.5%) male. The mean (standard error of the mean(SE)) IgE units for the group was 74.7 (5.5) IU/ml and the range 3-1 560 IU/ml. (Normal values are less than 150 IU/ml). Sixty-eight patients (11.1%) had total IgE values in excess of 150 IU/ml and the remainder (88.9 %) were within the normal range.

Positive skin reactions were found in 15 patients (2.4%). There were 7 (1.1%) positive reactions to lidocaine; 5 (0.8%) positive reactions to mepivacaine and 3 (0.5%) positive reactions to prilocaine. All these patients reacted favourably when challenged with another amide LA.

The clinical manifestations of the 'allergic events', as interpreted by the author are shown in Table I. Vasovagal attacks (syncope) are characterised by a transient vascular and neurogenic reaction marked by pallor, nausea, sweating, bradycardia and a rapid fall in blood pressure which, when below a critical level, results in loss of consciousness. It is often evoked by emotional stress associated with fear or pain.

Adrenaline may cause disturbing reactions such as fear, anxiety, tenseness, restlessness, throbbing headache, tremor, weakness, dizziness, pallor, palpitations and respiratory difficulty. These reactions manifest as apprehension, tachycardia, sweating, pounding in the chest and a choking sensation, and are all too often attributed erroneously to the LA and misdiagnosed as 'allergic to LA'.¹

Table I. Diagnoses of the 'allergic events' (n=611)

Event	n (%)
Vasovagal	39 (6.4%)
Adrenaline-related	182 (29.8%)
Anaphylactoid	174 (28.5%)
Other ('toxic')	216 (35.4%)

Only seven patients (1.1%) gave a positive response to the question whether the services of a physician, paramedic or hospital were required when the adverse reaction occurred. This indicated that a serious reaction had occurred and most psychogenic reactions could be ruled out.

Other allergies, as reported by 320 (52.3%) of the referred patients were: penicillin 124 (20.3%); sulphonamides 54 (8.8%); morphine and related compounds 52 (8.5%); aspirin and non-steroidal anti-inflammatory drugs 45 (7.4%); and honey-bee venom 45 (7.4%).

One hundred and one (23.9%) questionnaires were returned. Fifty-eight DPs referred patients to the author for the investigation of the 'allergies'. All the DPs utilised the recommended LAs. Another 43 practitioners consulted the author about 'allergic' patients without referring them. Respondents were also asked whether

the service should be continued; 99% indicated that it should be. The mean number of units (ampoules) of LA used per week was 79.2 (SD 23.4) per DP.

Six cases (1%) referred were patients who experienced nausea, dizziness and/or skin eruptions after an LA was injected into open wounds on the hands or feet, or infiltrated into the skin for the purpose of skin biopsies. These signs and symptoms were reported to their DPs who referred them to the author. They all had negative reactions to IDT.

Sixty-seven per cent of patients (26/39) whose 'allergic event' was diagnosed as vasovagal were male. In a number of these cases, the patients experienced a vasovagal reaction while the IDT was in progress.

DISCUSSION

LAs belong to the most widely used class of drugs in dentistry and medicine. Both the answers given by DPs in the questionnaire and the information from an LA manufacturer in South Africa corroborate this statement. Despite the wide use of amide LAs, the incidence of true allergy is unknown. It has been widely accepted that less than 1% of all reactions to LA are allergic in nature.^{2,4} In this investigation it was found that 2.4% of referred patients reacted positively to IDT with one of the amide LAs. When a different amide LA was used in the challenge, no adverse reactions were noted indicating that there is no cross-sensitivity between the amide LAs. Troise *et al.*²⁰ reported the same observations.

The greater prevalence of females in this investigation (79.5%) is in accordance with figures reported by other authors.^{20,21} The author also found that a high percentage (37%) of these females' reactions were adrenaline-related. LA solutions with adrenaline concentrations of 10 and 12.5 µg/ml are available in South Africa. The use of LA with the latter concentration might be responsible for the high prevalence of 'hyperresponders' diagnosed by the author.²⁴

It was interesting to observe that only 3 of the 15 patients who demonstrated positive skin reactions had total IgE values in excess of 150 IU/ml. In the remaining 12, values were within the normal limits. This is in accordance with Nettis *et al.*'s²¹ statement that the risk of adverse reactions to LAs is no greater in subjects with total IgE values in excess of the normal range than in those within the normal limits.

In cases where LAs are injected directly into skin wounds or the skin is infiltrated for biopsy purposes, the LA used in most of these cases is from multiple-dose vials. Usually these vials contain methylparaben as a bacteriostatic agent and no vasoconstrictor. The use of methylparaben in LAs used by DPs fell into disuse during the 1980s. The adverse reactions experienced by these patients could possibly be ascribed to the presence of a bacteriostatic drug or the absence of a vasoconstrictor.

Another adverse reaction is likely to be caused by the antioxidant in the LA solution. All dental LA solutions, containing one of the vasoconstrictors like adrenaline, noradrenaline or levonordefrin, contain an antioxidant to prevent their biodegradation by oxygen. Sodium or potassium metabisulphite or sodium bisulphate are the most frequently used antioxidants. Sulphites are well known to affect mainly asthmatics, and affect children more than adults. Approximately 10% of American adult asthmatics are sensitive to sulphites.²⁶

The protocol used in this study appears to be safe and can be utilised for the identification of an LA that can be used without risk. In all cases where patients' reactions to the IDT were negative, the referring practitioner

administered the recommended LA and no untoward reactions were reported.

CONCLUSION

This study demonstrates that the vast majority of patients referred by DPs and labelled as 'allergic to LA' are, in fact, not allergic. The author concurs with the view of Wasserfallen and Frei¹⁹ that improved diagnosis of LA allergy resulting in better patient selection could avoid most of these evaluations. However, since patients are usually very anxious after the appearance of the signs and symptoms of an 'allergic event', investigations of these adverse reactions might improve the tolerance of future LA administrations. Thus a useful service is offered to practitioners and patients who are fearful of possible LA allergies. The almost unanimous response from the questionnaire respondents indicates that this service is valued and should be continued.

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