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Anaphylactoid Reactions to Local Anaesthetics Despite IgE Deficiency : A Case Report

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SUMMARY **The mechanisms involved in adverse reactions to local anaesthetic (LA) agents are poorly understood. True IgE-mediated reactions appear to be rare. We report a patient with panhypogammaglobulinemia who developed anaphylactoid reactions to two different LAs (lignocaine and procaine), associated with positive intradermal skin tests to these agents as well as prilocaine, despite absent detectable IgE in the serum and a negative RAST test to procaine. We conclude that direct histamine release induced by LA is likely to be the major mechanism in this case.**

Adverse reactions to local anaesthetic (LA) agents are common but true allergic (IgE-mediated) reactions rare. [1,2] Some have challenged their existence. [3] Definition of these cases are clouded by complicating factors such as psychological reaction to the procedure or by toxic side-effects of the agents themselves. Testing in these patients is further complicated by the lack of knowledge of the pathophysiology of the reaction. There are reports of hypersensitivity reactions to LAs of types I, III and IV [4] as well as other, less well-defined reactions, any of which may be involved in individual patients. Several methodological and theoretical problems exist with the application of skin testing to patients with historical reactions. The nature of the hapten is unknown (whether the LA itself or a metabolite) and possible hapten-carrier complexes have not been identified. Further, the nature of the skin response varies from wheal and flare responses to local swelling, which may be immediate or delayed. We provide further evidence that IgE may not be involved in clinical anaphylaxis to LAs.

MATERIALS AND METHODS

Skin prick tests were performed in a standard fashion by placing a drop of the test solution on the volar aspect of the forearm and applying a skin prick through the drop with a 26 gauge hypodermic needle. The response was read at 15 minutes. Intradermal tests were performed using a 26 gauge hypodermic needle. Sufficient quantity of the test solution was injected to raise a 3 mm bleb (0.02 ml) and results were read at 15 minutes. For both tests, the wheal size was expressed as two diameters at right angles, and a positive result was defined as a dimension exceeding that of histamine 1 mg/ml for skin prick tests and 1 μg/ml for intradermal tests. A control solution of 0.9 percent saline was used in each test.

An IgE level was performed by immunoradiometric assay on two separate occasions, (one while on intramuscular replacement and one while on intravenous), both of which were 'trough' levels taken prior to an infusion, and were undetectable (< 1 IU/ml) on each occasion.

A RAST test for procaine was performed by standard technique. [5] This gave a negative result, although lacking a positive control.

CASE PRESENTATION

A 44 year old lady presented with anaphylactoid reactions to intramuscular lignocaine. At the age of 22 years (1969), recurrent pneumonia, bronchitis and otitis externa prompted immunoglobin estimation which showed panhypogammaglobulinemia consistent with common variable

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immunodeficiency. Replacement with intravenous gammaglobulin was commenced. Due to an anaphylactic reaction to the intravenous preparation four years later (1973) she was changed to intramuscular gammaglobulin administered with lignocaine (preservative-free) which was administered monthly.

After 11 years of this maintenance therapy (1984) she developed two mild reactions to the injections manifest by 5 minute episodes of chest tightness, subjective feelings of generalized warmth and difficulty in taking a deep breath. Injections were continued without incident for a further 18 months (1986) when a severe reaction occurred with chest discomfort, back pain and arthralgias, extreme hypotension (unrecordable blood pressure), cyanosis and respiratory arrest. A delayed diffuse, fine, erythematous rash followed the same day.

Skin prick and intradermal testing with lignocaine, prilocaine and methylparaben was performed (see method) after an interval of 6 weeks. Skin prick tests were negative, but intradermal testing was positive with both lignocaine and prilocaine (Table 1). Methylparaben gave no reaction on intradermal injection. Similar testing was subsequently performed with procaine, and only trivial flare reactions occurred to intradermal tests and subcutaneous challenge. Subsequent gammaglobulin was administered with procaine (preservative-free) with no adverse effects.

Because of ongoing recurrent infections and poor serum gammaglobulin levels, intravenous gammaglobulin (Sandoglobulin, Sandoz) was commenced 12 months later (1987) and anaphylaxis occurred on the first infusion. Intramuscular gammaglobulin and procaine were resumed one month later and a further reaction occurred on the first injection which consisted of facial flushing, postural faintness and general fatigue. Injections were ceased at the patient's insistence, and cimetidine was commenced in a attempt to boost gammaglobulin levels.[6] Repeat skin testing and subcutaneous challege with procaine was negative 2-3 weeks after the presumed reaction, however when repeated 4 months later, undiluted intradermal procaine induced a 6 × 6 mm wheal and 10 × 10 mm flare (Table 2). Further intramuscular gammaglobulin was given without local anaesthetic and no reactions took place. She was subsequently

Table 1. LA skin testing after initial adverse reactions, showing positive responses to lignocaine and prilocaine, but only trivial flare reactions to incremental challenge with procaine.

Histamine response was 4x4 for intradermal injection.

Local anaesthetic	Concentration	Skin test	Response
Lignocaine	1:100	Skin prick	neg
	1:10		neg
	Undiluted		neg
	1:100	Intradermal	5x5mm wheal
	1:10		6x6mm wheal
Prilocaine	1:100	Skin prick	neg
	1:10		neg
	Undiluted		neg
	1:100	Intradermal	5x5mm wheal
	1:10		6x6mm wheal
Methylparaben	Undiluted	Skin prick & Intradermal	neg
Procaine	1:100	Skin prick & Intradermal	neg
	1:10		
	Undiluted		
	Undiluted	Subcutaneous Incremental challenge:	
		0.5ml	neg
		1ml	10x10mm flare
		2ml	20x20mm flare

Table 2. Procaine skin testing after second LA reaction, showing a positive reaction to undiluted procaine.

Local anaesthetic	Concentration	Skin test	Response
Procaine	1:100	Skin prick	neg
	1:10		
	Undiluted		
	1:100	Intradermal	neg
	1:10		neg
	Undiluted		6x6mm wheal & 10x10mm flare

converted back to intravenous gammaglobulin (Intragam, Commonwealth Serum Laboratories) which continues to be well-tolerated. Skin prick testing to a battery of common inhaled aeroallergens was negative.

DISCUSSION

LA anaphylactoid reactions are rare, and it is of interest that they occurred in this patient despite the absence of detectable total and specific IgE. The historical reactivity to both lignocaine and procaine (and prilocaine on skin testing) is also noteworthy, especially for the fact that it would not have been predicted on the basis of cross-reacting LA groups (see below). The reaction after reinstituting the intramuscular injections after a two-month break in 1987 suggests that the monthly exposure to procaine may have had a desensitising effect.

The mechanisms involved in clinical anaphylactic reactions to LAs have been poorly defined. Immediate reactions associated with positive skin tests certainly suggest IgE-mediated hypersensitivity, and passive transfer of reactivity has been reported, although all but one of the reports have suffered from inadequate reporting or methodological problems.[4] This patient's LA reactions and positive skin tests suggest IgE-mediated anaphylaxis, yet she lacked detectable serum IgE and had a negative RAST to procaine. Direct stimulation of mast cells or basophils to release histamine or other mediators is therefore the most likely mechanism in this case. Minute quantities of LA-specific high-affinity IgE may exist below the threshold for detection which could be responsible for the reactions. This appears unlikely, but cannot be entirely excluded by the negative RAST, which lacked a positive control. It is also possible that trace quantities of LA-specific IgE contaminated the replacement gammaglobulin[7,8] and was responsible for the reaction. The absence of similar reactions in other patients receiving pooled blood products and the low levels of total IgE in gammaglobulin preparations make this possibility unlikely. Anaphylactoid reactions can occur in patients receiving pooled gammaglobulin preparations, usually in the setting of intravenous infusion rather than intramuscular injection, thought to be related to gammaglobulin aggregates activating circulating complement components. This is unlikely to occur by the intramuscular route unless there was inadvertant puncturing of a larger blood vessel with subsequent direct systemic injection. The positive LA skin tests and the cessation of the reactions when gammaglobulin was given without LA suggest that this is an unlikely explanation.

Watkins[9] has hypothesised that anaphylactoid responses which occur in the presence of low IgE levels may be related to two possible mechanisms. IgE binding to mast cells may be of normal affinity, but low serum IgE levels leave receptor sites unoccupied with the propensity for direct physicochemical stimulation and activation. Alternatively, IgE-binding may be of high affinity and mast cell activation occurs via the specific interaction between IgE and ligand despite low levels of total IgE in the serum. Both mechanisms could be operative in our report, however the negative RAST to procaine would favour the former mechanism over the latter.

Ours is a further case where a positive history correlated with positive skin tests, although the clinical significance of her reaction to prilocaine was not tested by challenge. The diagnostic usefulness of positive skin tests in assessing adverse reactions to LA has been challenged,[2,10] however there are many reports similar to ours of correlation between positive histories and positive skin tests.[4]

Our patient also demonstrated skin-test cross-reactivity at initial testing between lignocaine and prilocaine, both group II LAs,[4] and subsequently developed a reaction to procaine, a benzoic acid ester classified with group I. These groups had initially been proposed on the basis of chemical structure[11] and apparent cross-reactivity in contact dermatitis and patch-testing.[12,13] The validity of the classification was supported by Schatz[4] in a review of adverse LA reactions of a more generalized nature. In this classification, cross-reactivity is said to occur between the class I LAs, but not between class I and class II LAs, nor between different class II drugs. In his literature review of 33 patients, all 31 that were tested then challenged with an LA predicted by cross-reacting groups had a negative reaction. Although our patient initially tolerated the predicted agent (procaine), it was of interest that reactivity subsequently developed to this drug also, despite belonging to the opposite class. There was also skin test (but not historical) reactivity between two of the class II agents (lignocaine and prilocaine), which is not uncommon.[2]

We conclude that anaphylactoid reactions with positive skin tests to local anaesthetic agents may occur in the absence of detectable IgE. The pathogenesis of these reactions most likely relates to direct histamine release from mast cells.

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