Editorial

Immediate Local Anesthetic Reactions: Too Quick to Point the Finger?

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Local anesthetics (LA) are commonly used across medical specialties for procedures ranging from dental work and skin biopsies to endoscopies and major surgical procedures. They work by stabilizing neuronal membranes and inhibiting the transmission of neural impulses, allowing procedures to be performed safely and painlessly. LA have been used since it was discovered in 1884 that cocaine could anesthetize the human cornea.[1] They are now widely available worldwide and administered as an injectable or topically.

Given their widespread use, there is legitimate concern for hypersensitivity reactions. Delayed-type hypersensitivity reactions, particularly allergic contact dermatitis, have been well described, and patch testing can help to accurately identify sensitization, allowing for avoidance.[2] In fact, the prevalence of allergic contact dermatitis to LA may be rising.[3,4] The prevalence of IgE-mediated allergic reactions has been less clearly defined, as adverse reactions are common and can mimic a hypersensitivity reaction. Epinephrine is commonly coadministered to increase local duration of action and prevent systemic absorption and can lead to palpitations and tachycardia, tremulousness, headaches, and other symptoms that can be confused with a hypersensitivity reaction. In addition, vasovagal responses, anxiety, toxic reactions such as dysrhythmias, and reactions to additives and preservatives such as methylparabens can cause confusion and lead to concern for an IgE-mediated reaction. True IgE-mediated allergic reactions are rare and are estimated to be <1% of all reported reactions.[5] Despite this, physicians and patients commonly mistake these adverse reactions for hypersensitivity, and overestimate the prevalence of IgE-mediated allergy.

In a systematic review of case series, true IgE-mediated allergy to an LA was identified in 29 of 2978 patients.[6] However, only 19 patients had a positive challenge, and, of these, many were local reactions at the site of administration. For example, in a study by Gall et al[7] that was included in the review, 177 patients with a history of an adverse reaction to LA underwent skin testing and challenge. Three had positive challenges, with 1 with a delayed-type hypersensitivity reaction and 2 with itchy wheals and erythema at the injection site and on the trunk, which resolved spontaneously within 2 hours. In a study by Berkun et al, also included in the review, 236 patients underwent evaluation for LA allergy by skin testing and challenge. One patient had a reportedly positive challenge, though only local erythema at the injection site was noted.[8] Patients were often challenged to an unrelated local anesthetic to identify an LA that can be used for subsequent procedures. Although this is helpful clinically, it overestimates the true prevalence of hypersensitivity reactions and leads patients to believe that they are truly allergic to the original LA, despite the likelihood of tolerance on rechallenge.

In the study of LA allergy by Kvisselgaard et al[9] in this issue of *JACI-in-Practice*, 164 patients with suspected local anesthetic allergy were evaluated with 189 challenges, and all challenges were negative. Patients with perioperative reactions were excluded, and the authors have previously published data that did not identify any LA allergy in a cohort of patients with perioperative anaphylaxis.[10] Patients with a history of a nonimmediate reaction, defined as a reaction with a delayed presentation causing only skin symptoms, were also excluded, which limits the applicability of this study to these patients. The culprit drug was tested if known, and high-risk patients underwent a dose escalation challenge. Patients were identified by hospital coding, and this has the potential to miss patients due to the inconsistencies in coding and the need to use specific and nonspecific codes to fully identify patients. Skin testing was only completed in 12% of patients, and all were negative. Other potential allergens were also tested, although not systematically, and another allergen was confirmed in 10% of patients, with antibiotics and nonsteroidal anti-inflammatory drugs as the most commonly identified culprit. By extrapolating their data, they conclude that the incidence of LA allergy must be less than 1 in 1.2 million patients.

LA can be classified into 2 categories, esters and amides, and reactions to esters have been more commonly identified historically, likely secondary to their para-aminobenzoic acid metabolites.[11] This has led to increased use of amides to avoid reactions. Ester LA are rarely used in Denmark, and it is notable that in the Kvisselgaard et al study there were no patients who underwent testing or challenge with an ester LA.

The identification of other allergens is an important finding and a reminder that other exposures during a procedure should be considered in the evaluation of a patient with a possible LA allergic reaction. In addition to medications administered such as antibiotics and analgesics, exposures to latex and chlorhexidine can be important causes of the reaction. Latex and chlorhexidine are well known to cause IgE-mediated reactions in the perioperative setting and have also been confirmed as the culprit allergens in patients with suspected LA reactions. In a study of 135 patients who underwent evaluation for LA allergy, 7% of the patients were diagnosed with IgE-mediated allergy to another substance, 5 of the 10 patients to chlorhexidine and 3 of the 10 patients to latex.[12] Of the 2 patients who had suspected local

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anesthetic hypersensitivity, one had a delayed hypersensitivity reaction and the other had a "scarce but generalized itching urticaria" that could be consistent with an IgE-mediated reaction. Mast cell disorders are also a potential confounder and should be considered, as 3 patients with mast cell disorders were identified in an evaluation of perioperative anaphylaxis.[13]

This study highlights the need for a complete evaluation of patients with suspected allergic reactions to LA, including other possible allergens that may have been administered during the procedure, such as antibiotics and analgesics, as well as external exposures such as latex and chlorhexidine. It is clear that local anesthetics can cause delayed-type hypersensitivity but, given the increasing evidence that IgE-mediated allergy is very rare, testing to the suspected LA is safe and important.

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