



Letter

The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions

Anaphylaxis in association with anesthesia and surgery is a rare but potentially life-threatening event. To avoid repeat episodes, it is important to identify the causative agents.

Different agents have been implicated as causes of anaphylaxis during anesthesia. The most prominent are the neuromuscular blocking drugs, latex, and antibiotics. Of increasing interest, however, is the antiseptic agent chlorhexidine. Chlorhexidine is an antiseptic found in a wide variety of products in the perioperative setting and in many household products.^{1,2} Such widespread availability potentially increases the risk that patients might be sensitized before surgery.

Skin testing is the standard diagnostic tool used to investigate causative agents in perioperative allergic episodes.

In addition to skin testing, laboratory methods for the investigation of chlorhexidine allergy include measurement of allergen specific IgE (sIgE). A commercial assay for sIgE to chlorhexidine is available, but studies evaluating this assay have been limited to date, with only 1 other evaluation in a large patient group.³

Therefore, the aim of this study was to evaluate and optimize chlorhexidine sIgE testing in cases of perioperative allergy.

A total of 130 patients were included in this retrospective analysis of routine clinical investigations. All had been referred to the Anaesthetic Allergy Referral Service, Royal North Shore Hospital (Sydney, Australia) for investigation and were selected based on a clinical presentation that included chlorhexidine as a possible causative agent of a perioperative allergic event. Patients were assessed from June 2009 to August 2013 (66 women, 64 men; median age 56.5 years).

Intradermal and skin prick testing was performed according to a standardized protocol with all suspected agents to which patients had been exposed (eMethods).

Measurement of sIgE to chlorhexidine and total IgE in patient serum was carried out on samples collected at the time of skin testing using the ImmunoCAP system (Phadia AB, Uppsala, Sweden). Statistical analysis was performed using Analyse-it for Excel 2.30 (Microsoft, Redmond, Washington). This included receiver operating characteristic curve analysis and sensitivity and specificity determinations.

The study was approved by the local health district human research ethics committee.

Of the 130 patients, 19 had positive prick and/or intradermal skin test reactions for chlorhexidine. Negative skin test results were displayed in 111 patients.

The median concentration of chlorhexidine sIgE in the patients with positive skin test reactions was 1.23 kU_A/L (range 0.14–11.90)

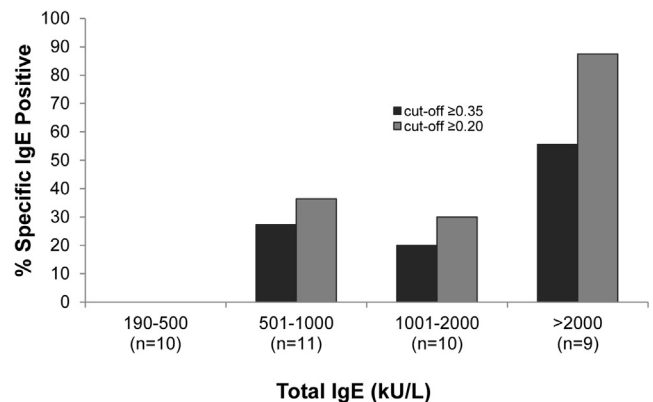


Figure 1. Proportion of positive chlorhexidine-specific IgE results for serum samples at varying total IgE levels. Manufacturer-recommended and receiver operating characteristic generated cutoff thresholds are compared.

compared with the median concentration in the patients with negative skin test reactions of 0.10 kU_A/L (range 0.10–3.05).

Using the recommended cutoff value of 0.35 kU_A/L, sIgE to chlorhexidine showed a sensitivity of 84.2% with reference to skin test results and a specificity of 93.7%. Positive predictive value was 69.6% and negative predictive value was 97.2%.

An alternative cutoff threshold of 0.20 kU_A/L was determined by receiver operating characteristic analysis. This increased the sensitivity to 94.7% but only slightly decreased the specificity to 90.1%. The corresponding positive predictive value was 62.1% and the negative predictive value was 99.0%.

When using only the standard cutoff threshold, 1 patient produced a negative sIgE result on a sample taken at the time of the initial clinical reaction but exhibited a much increased level of chlorhexidine sIgE at the time of skin testing 3 weeks later. This highlights the potential utility of a lower threshold, particularly in cases in which early sIgE testing might be necessary. Further studies examining the timing aspect of chlorhexidine sIgE testing need to be performed.

A correlation was noted between chlorhexidine sIgE and total IgE levels ($r_s = 0.610$, $P < .001$, Spearman test). To determine whether high total IgE levels might lead to falsely increased sIgE levels, results from 50 patients with inhalant allergy and high total IgE were evaluated.

Results comparing the proportions of samples with positive chlorhexidine sIgE levels at varying total IgE concentrations are shown in Figure 1.

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Using a cutoff threshold of 0.35 kU_A/L, chlorhexidine sIgE was positive in 56% of samples with a total IgE level higher than 2,000 kU/L (n = 9), 20% of samples with a total IgE level of 1,001 to 2,000 kU/L (n = 10), 27% of samples with a total IgE level of 501 to 1000 kU/L (n = 11), and 0% of samples with a total IgE level of 190 to 500 kU/L (n = 10).

Lowering the threshold to 0.20 kU_A/L to increase sensitivity resulted in positive sIgE levels for 3 additional samples among those with a total IgE level higher than 2,000 kU/L and 1 additional sample in each group with total IgE levels of 1,001 to 2,000 kU/L and 501 to 1,000 kU/L. No change was observed in the remaining group.

Previous studies have indicated that total IgE levels of at least 1,500 kU/L could interfere with quantitation of sIgE in the ImmunoCAP system in some assays.⁴ This study suggests that raised total IgE levels can have an impact on chlorhexidine sIgE measurement at levels higher than 500 kU/L and more particularly at levels higher than 2,000 kU/L. In the absence of skin testing or allergen challenge; however, the fact that some patients with inhalant allergy could have been sensitized to chlorhexidine cannot be discounted, particularly because of the ubiquitous nature of chlorhexidine-containing products.²

Although chlorhexidine sIgE measurement correlated well with skin test results, it should be remembered that skin testing itself might not exhibit 100% sensitivity and specificity.^{5,6} The positive predictive value of 69.6% (or 62.1% at the lower threshold) might reflect the effect of raised total IgE on the sIgE test or might indicate allergy in patients not detected by skin testing. Of the patients with negative skin test reactions but positive chlorhexidine sIgE reactions, 2 had a clinical picture consistent with chlorhexidine allergy. For this reason, we concur with suggestions that a combination of diagnostic methods is advisable in association with the clinical history.^{3,7}

With respect to the high sensitivity and specificity seen with the chlorhexidine sIgE assay, a positive result in the context of a low total IgE level might be sufficient for a diagnosis of chlorhexidine allergy in some settings. This particularly might be the case where there is a strong clinical history or in cases in which skin testing is unclear or unable to be performed. However, it should be noted that sensitivity and specificity were evaluated using sIgE measurements determined on serum samples collected at the time of clinic attendance for skin testing. Therefore, the timing of a serum test might be relevant to the utility of this protocol, particularly in view of the need for further studies in this area as previously mentioned.

Overall, our evaluation of sIgE testing to chlorhexidine by the ImmunoCAP method shows this to be a reliable diagnostic method to use in addition to skin testing in the investigation of perioperative allergy. Adjustment of the cutoff threshold also can increase sensitivity without significantly affecting specificity. However, results should be evaluated with caution in the presence of total IgE levels higher than 500 kU/L and particularly at levels higher than 2,000 kU/L.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.02.002>.

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eMethods*Skin Testing Protocol*

Positive and negative controls were established intradermally with morphine and 0.9% saline, respectively. Skin testing was performed on the forearm with chlorhexidine gluconate with cetrimide (Pfizer Australia, West Ryde, Australia). (We note that the presence of the antiseptic cetrimide in the chlorhexidine solution used for skin testing could contribute to a positive skin test reaction in the absence of chlorhexidine allergy and detectable chlorhexidine specific IgE. However, we also note that no

reports of immediate hypersensitivity reactions to cetrimide are apparent in the literature.) The concentration of chlorhexidine used for intradermal testing was 0.00002%. For skin prick testing, the concentration was 0.05%, escalating if necessary to 2%. All solutions were prepared under sterile conditions at the time of clinic attendance by patients. Intradermal testing involved injection of approximately 0.02 mL of chlorhexidine solution to produce a wheal 3 to 4 mm in diameter. Tests were interpreted at 20 minutes. A response was considered positive when wheal diameter exceeded 8 and 3 mm for intradermal and skin prick tests, respectively.