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CASE REPORT OPEN ACCESS

Reevaluating the timing of specific immunoglobulin E measurement after anaphylaxis

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Abstract
The anergic period is defined as a period of around 3-6 weeks following a systemic allergic reaction when skin test results are negative. Therefore, most guidelines recommend that physicians should conduct skin test 6 weeks after an immediate hypersensitivity reaction. However, in vitro tests, including serum-specific immunoglobulin E (IgE) measurement, are generally deemed unaffected by the anergic period. Here, we present a case of a patient with initial cefaclor-specific IgE negativity, but when tested immediately after confirmed anaphylaxis to cefaclor, the results converted to positive after the resolution of the anergic period, 8 weeks post reaction. In patients with a strong clinical suspicion of drug-induced anaphylaxis, repeating in vitro tests after the anergic period may be warranted, even if the initial results are negative. Further investigation is needed to assess whether ImmunoCAP values, similar to skin test reactivity, exhibit significant short-term variability.

Introduction

Allergen-specific immunoglobulin E (IgE) measurement forms the cornerstone in the diagnosis of immediate hypersensitivity reactions, and also used to test drug-induced hypersensitivity.[1,2] To evaluate immediate hypersensitivity drug reactions, several diagnostic methods are available, including skin tests (e.g., skin prick and intradermal tests), measurement of drug-specific IgE in serum, and drug provocation tests.[2] The fluorescent enzyme immunoassay (ImmunoCAP®, Thermo Fisher Scientific Inc., Waltham, MA, USA) is a widely used commercial method for detecting drug-specific IgE.[2] Cefaclor-specific IgE can be assessed in patients with suspected immediate hypersensitivity reactions using the automated ImmunoCAP enzyme-linked immunosorbent assay (ELISA) system.[3]

In patients with anaphylaxis, skin tests are recommended at least 6 weeks after the reaction to account for

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the anergic period.[2,4] This phenomenon has traditionally been described in the context of insect venom allergy.[2] In contrast, serum-specific IgE testing can theoretically be performed at any time after the reaction;[2] however, it is unclear whether serum-specific IgE detection is truly unaffected by the anergic period or if repeat testing after an appropriate interval is warranted.

Here, we report a case of a patient who tested negative for cefaclor-specific IgE on the day of an anaphylactic episode, but demonstrated a positive result upon retesting 8 weeks later, reflecting a temporal change in the immunologic response. This case challenges the assumption that in vitro IgE testing is unaffected by the anergic period and suggests the need for reassessment of ImmunoCAP timing.

Case Presentation

A 70-year-old woman presented with symptoms that developed 30 minutes after taking prescribed medications (cefaclor, rebamipide, and loxoprofen) following a dental procedure. She had previously taken the same medications, including cefaclor, during a dental procedure 1 year earlier without any adverse reaction. The patient experienced generalized urticaria with severe pruritus 30 minutes after medication administration, followed by throat tightness, chest discomfort, abdominal pain, and an urge to defecate. She contacted emergency medical services (EMS); however, EMS personnel found the patient unconscious and unresponsive to painful stimuli and was subsequently transported to the emergency department. Upon arrival, the patient's vital signs were recorded as follows: blood pressure 70/40 mmHg; oxygen saturation 88%; heart rate 109 bpm; and body temperature 36.6°C and promptly treated with intramuscular epinephrine (0.3 mg), intensive fluid resuscitation, supplemental oxygen, intravenous methylprednisolone (40 mg), and intravenous chlorpheniramine (2 mg). Her condition resolved completely within an hour and regained a fully alert mental status. Blood samples were collected from the patient 60 minutes after the event to assess serum tryptase- and cefaclor-specific ImmunoCAP levels. The analysis revealed a significant elevation in serum tryptase (22.3 μg/L compared to the baseline value of 4.96 μg/L), whereas the cefaclor-specific ImmunoCAP level was measured at 0.27 kUA/L. For ImmunoCAP assays, allergen sIgE values ≥ 0.35 kU_A/L were considered positive.[5]

Given the timing of drug administration, cefaclor-induced anaphylaxis was considered to be the most likely cause, after which the patient was referred to our allergy clinic. Eight weeks after the anaphylactic episode, the patient underwent a workup at our allergy clinic to investigate the cause of anaphylaxis. The skin prick and intradermal tests were performed using cefaclor with maximum concentrations (2 mg/mL) prepared in compliance with the guidelines established by the European Academy of Allergy and Clinical Immunology;[2] the results were unequivocally negative. In this patient, the acute allergic reaction was classified as Grade 5,[6] the highest severity level, making the drug provocation test unfeasible despite the negative skin test and ImmunoCAP results. The patient was advised to avoid all medications taken at the time of the anaphylaxis.

Based on a study reporting extended anergic periods beyond the typical duration,[7] repeated ImmunoCAP and skin tests were performed 12 weeks after the initial episode, confirming anaphylaxis. The skin test results remained negative; however, ImmunoCAP was detected at a level of 2.3 kUA/L. For further investigation, drug provocation tests were conducted using loxoprofen and rebamipide, which elicited no adverse reactions. Based on a comprehensive evaluation of the diagnostic findings, the patient was diagnosed with cefaclor-induced anaphylaxis. Repeat skin tests were performed at 6 months after the initial episode, but the results were still negative with cefaclor. The patient provided written informed consent for the use of her medical data.

Discussion

The concept of an anergic period following anaphylaxis is well-established.[2,7] Skin tests performed during this period may yield false-negative results; therefore, most guidelines recommend that physicians should consider performing skin tests 3–6 weeks after the event[2]; however, in vitro anaphylaxis tests are generally recommended as soon as possible.[2]

Skin test refractoriness is thought to result from the depletion of mast cell mediators following a systemic allergic reaction,[7] but skin test guidance is primarily based on expert consensus rather than robust clinical evidence.[2] Notably, a study documented patients in whom skin test results remained negative at 8 weeks but became positive upon retesting at 6 months.[7] Thus, in patients for whom clinical suspicion persists, skin tests should be repeated beyond 8 weeks and 6 months after the reaction.

The ImmunoCAP assay uses a singleplex approach to quantify IgE levels specific to a selected allergen analyte and operates on the principle that allergen-specific IgE antibodies present in the serum bind to allergens coupled in excess to a solid phase.[1] The design of the singleplex ImmunoCAP facilitates the complete binding of IgE antibodies, thus providing high sensitivity over a broad linear range.[1] This assay is widely regarded for its reliable and accurate quantification.[1] However, ImmunoCAP testing for drug allergy is restricted to a limited range of allergens (benzylpenicillin (penicillin G), penicillin V, amoxicillin, ampicillin, and cefaclor.[2] Further research is needed to validate the utility of ImmunoCAP in diagnosing immediate drug hypersensitivity reactions. The basophil activation test is another in vitro method used to evaluate immediate drug hypersensitivity reactions; however, it could not be performed in this case since it is not commercially available in Korea.[8]

This is the first report to document a patient in whom drug-specific IgE results transitioned to positive after the anergic period. These findings suggest that in vitro testing for drug-specific IgE may require reassessment after the resolution of the anergic period.

In Korea, the incidence of immediate hypersensitivity reactions, especially anaphylaxis, to cefaclor has been rising, prompting increased attention toward improving diagnostic accuracy for this condition.[9,10] Accordingly,

several studies have explored the possibility of lowering the ImmunoCAP cutoff value for cefaclor to 0.1 kU/L, a threshold that would have rendered the initial result in this patient as positive.[11,12] However, lowering the cutoff value to 0.1 kU/L has not been widely implemented due to concerns regarding a significant reduction in specificity and limited supporting evidence.[11,13] Considering the potential limitations of lowering the ImmunoCAP cutoff to 0.1 kU/L and the findings of this case, reassessing the need for repeat test may be warranted, even when the initial ImmunoCAP result is negative.

Furthermore, in this patient, the ImmunoCAP results presented a significant increase following the anergic period, which cannot be solely attributed to the cutoff value. Although drug-specific IgE is known to decrease over time,[14] in this patient, the test values increased 8 weeks post reaction, which resulted in reclassification to a positive result. Similar to the temporal changes observed in skin test reactivity, further research is warranted to elucidate the time-dependent dynamics of drug-specific IgE levels. Furthermore, investigating these changes may provide insights into the variability in the duration of drug allergies among individual patients.

Conclusion

In conclusion, this study is the first to highlight that ImmunoCAP results may undergo significant changes following the anergic period after anaphylaxis. This observation challenges the conventional practice of testing immediately after the reaction. Repeated in vitro testing may be warranted in patients with a strong suspicion of drug-induced anaphylaxis. Further studies are required to explore the temporal dynamics of ImmunoCAP values and their clinical implications.

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Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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