Original Article

Epinephrine Use in Positive Oral Food Challenges Performed as Screening Test for Food Allergy Therapy Trials

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What is already known about this topic? Oral food challenges (OFCs), the gold standard for the diagnosis of food allergy, have known risks as symptoms can range from mild to potentially life-threatening.

What does this article add to our knowledge? The results of this study indicate a high rate epinephrine treatment for diagnostic food challenges used to screen for entry into food therapeutic trials.

How does this study impact current management guidelines? Diagnostic OFCs for food therapeutic trials are safe when performed by experienced personnel. Although many require epinephrine treatment, few require multiple doses of epinephrine, and biphasic reactions are infrequent.

BACKGROUND: Previous studies report epinephrine use for positive oral food challenges (OFCs) to be 9-11% when generally performed to determine outgrowth of food allergies. Epinephrine use for positive OFCs performed as screening criteria for enrollment in therapeutic trials for food allergy has not been reported.

OBJECTIVE: The objective of this study was to assess the characteristics and treatment for positive OFCs performed for screening subjects for food therapeutic trials.

METHODS: Retrospective review of positive screening OFCs from 2 treatment trials, food allergy herbal formula-2 (n = 45) and milk oral immunotherapy (n = 29), conducted at the Icahn School of Medicine at Mount Sinai was performed.

RESULTS: The most common initial symptom elicited was oral pruritus, reported for 81% (n = 60) of subjects. Overall, subjective gastrointestinal symptoms (oral pruritus, throat pruritus, nausea, abdominal pain) were most common (97.3% subjects), followed by cutaneous symptoms (48.7%). Of the 74 positive double-blind, placebo-controlled food challenge, 29 (39.2%) were treated with epinephrine; 2 of these subjects received 2 doses of epinephrine (6.9% of the reactions treated with epinephrine or 2.7% of all reactions). Biphasic reactions were infrequent, which occurred in 3 subjects (4%).

CONCLUSIONS: Screening OFCs to confirm food allergies can be performed safely, but there was a higher rate of epinephrine use compared with OFCs used for assessing food allergy outgrowth. Therefore, personnel skilled and experienced in the recognition of early signs and symptoms of anaphylaxis who can promptly initiate treatment are required. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Epinephrine; Positive oral food challenge; Anaphylaxis; Food allergy*

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Clinical Trial Registration: Therapeutic Effect of Chinese Herbal Medicine on Food Allergy (FAHF-2); ClinicalTrials.gov Identifier: NCT00602160. OIT and Xolair® (Omalizumab) in Cow's Milk Allergy; ClinicalTrials.gov Identifier: NCT01157117.

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Abbreviations used
OFC- Oral food challenge
FAHF-2- Food allergy herbal formula 2
SPT- Skin prick test
DBPCFC- Double-blind, placebo-controlled food challenge
IVF- Intravenous fluid

Oral food challenges (OFCs) are the gold standard for the initial diagnosis of food allergy. As the search for an effective treatment for food allergy has expanded, OFCs are being performed more frequently to ensure that individuals enrolled into these clinical trials are currently reactive to the allergen. OFCs have inherent risks as symptoms can range from mild to potentially life-threatening. Unfortunately, severity of reactions cannot be predicted by skin prick tests[1] or food-specific IgE levels.[2-4] Thus, experienced personnel are essential to ensure that symptoms are recognized quickly and treatment initiated promptly to optimize outcomes.

Several studies have been reported on the safety of OFCs performed for determining whether food allergies have been outgrown. In these studies, rates of epinephrine use have ranged from 9% to 11% for positive challenges,[5-7] and biphasic reactions have been uncommon.[6,8] However, there is little information regarding the safety of OFCs performed to confirm food allergy for entry into food therapy clinical trials.

We sought to characterize the positive OFCs performed as screening for food therapeutic trials.

METHODS

Subjects

Subjects with positive screening double-blind, placebo-controlled oral food challenges (DBPCFCs) performed for enrollment in the food allergy herbal formula 2 (FAHF-2) and milk oral immunotherapy (MOIT) therapeutic trials performed in the Clinical Research Unit between October 2010 and September 2012 at Icahn School of Medicine at Mount Sinai were included. These studies excluded those with a history of life-threatening anaphylaxis to milk, peanut, tree nut, sesame, fish, or shellfish (involving hypotension or requiring mechanical ventilation). Information related to prior reactions to the food as well as prior treatment with epinephrine was obtained. Charts were reviewed for details including age, gender, comorbidities such as asthma, specific IgE levels and skin prick test results, foods challenged, symptoms, and treatments given.

Skin prick test

Skin prick tests (SPTs) were performed with GreerPicks by using glycerinated food extracts (Greer Laboratories, Inc., Lenoir, NC) and a saline and histamine control. The size of the skin test response was calculated as a mean of the longest diameter and its longest orthogonal diameter measured at 10 to 15 minutes.

Serum-specific IgE measurements

Sera were analyzed for antigen-specific IgE antibody concentrations with the ImmunoCAP System (ThermoFisher Scientific, Waltham, Mass). Results were expressed as kU_A/L of a specific IgE antibody.

Double-blind, placebo-controlled oral food challenges

DBPCFCs were performed by feeding gradually increasing amounts of the food allergen at 10- to 15-minute intervals under supervision, as outlined in each protocol. The subjects were off antihistamines for an appropriate length of time (5 half-lives of the antihistamine). Before the DBPCFC, subjects were assessed for an excerbation of asthma as determined by active wheeze or a peak expiratory flow rate <80% predicted. A uniform approach was used for food challenges. The DBPCFC consisted of a total of 2 g protein of the food allergen, distributed in the following manner: 1, 5, 15, 50, 75, 100, 250, 500, and 1000 mg.

Frequent assessments were made. A food challenge was considered positive when a subject developed cutaneous (urticaria, angioedema, and/or flushing), gastrointestinal (abdominal cramping, vomiting, and/or diarrhea), respiratory (persistent nasal congestion, persistent rhinorrhea, persistent sneezing, tightness in the throat, dysphonia, dyspnea, and/or wheezing), and/or cardiovascular (dizziness, loss of consciousness, and/or hypotension) symptoms. DBPCFCs were also stopped if the subject had persistent subjective symptoms.

When the challenge was terminated for a reaction, the subject was treated with medications (ie, epinephrine, antihistamine, corticosteroids) as deemed appropriate by the study physician. Subjects remained under observation for at least 4 hours after the reaction as a precaution against recurrent late reactions. Biphasic reactions were classified as those with recurrence of symptoms after resolution of the initial event in 1 to 78 hours.[9]

Informed consent was obtained from the participants, and the clinical trials were approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai, New York, NY.

Statistics

Data were analyzed by using GraphPad (GraphPad Software, La Jolla, Calif.). The Mann-Whitney rank-sum test was used for comparisons of medians and the t test for comparisons of means. The χ^2 test and Fisher exact test were applied to determine differences in proportions. A P value $<.05$ was considered statistically significant.

RESULTS

Subjects

There were a total of 74 positive DBPCFCs. The median age was 13 years (range 7-40 years), and 32.4% were females. This was a highly atopic group, with 85% having multiple food allergies, 78.4% had a history of asthma, 35.1% had a history of anaphylaxis, and 33.8% previously received epinephrine to treat an allergic reaction. The median allergen-specific IgE was 30 kU_A/L (range 0.59 to >100) and the median SPT wheal diameter was 8.5 mm (range 2-17.5).

Symptoms

The most common initial symptom at reaction was oral pruritus, reported for 81% (n = 60) of subjects. This symptom was not dose-limiting; thus, all of these subjects continued the food challenge and received subsequent doses. No challenge was stopped solely for oral pruritus. Throat pain and/or tightness were the first symptoms for 8.1% and abdominal pain was the symptom for 4%.

Overall, subjective gastrointestinal symptoms (oral pruritus, throat pruritus, nausea, abdominal pain) were the most common