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

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Abstract

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—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 two treatment trials, Food Allergy Herbal Formula-2 (FAHF-2) (n=45) and Milk Oral Immunotherapy (MOIT) (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 DBPCFCs, 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, occurring 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 to 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.

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Keywords

Epinephrine; positive oral food challenge; anaphylaxis; food allergy

Introduction

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. Oral food challenges 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 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 9–11% 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 performed for enrollment in the Food Allergy Herbal Formula 2 (FAHF-2) and Milk oral immunotherapy (OIT) 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). Results were expressed as kU_A/L of specific IgE antibody.

Double-blind, placebo-controlled oral food challenges (DBPCFC)

DBPCFCs were performed by feeding gradually increasing amounts of the food allergen at 10–15 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). Prior to the DBPCFC, subjects were assessed for an exacerbation 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 grams 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 (i.e. epinephrine, antihistamine, corticosteroids) as deemed appropriate by the study physician. Subjects remained under observation for at least 4 hours following 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, CA). 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 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 for 4%.

Overall, subjective gastrointestinal symptoms (oral pruritus, throat pruritus, nausea, abdominal pain) were the most common symptoms, affecting 97.3% subjects. Other symptoms included cutaneous (48.7%), upper respiratory tract (sneezing, rhinorrhea) (31.1%), lower respiratory tract (wheezing, cough, stridor) (56.8%), objective gastrointestinal (emesis, diarrhea) (27.0%), cardiovascular (5.4%) and neurological (5.4%). Neurological symptoms were described as a feeling of weakness or of feeling faint.

Treatments

Epinephrine was used as treatment for symptoms in multiple body systems, respiratory symptoms, throat tightness and/or severe abdominal pain and cramping as outlined in each of the protocols. Of the 74 positive DBPCFCs, 29 (39.2%) were treated with epinephrine. Two of these subjects were given 2 doses of epinephrine (6.9% of the reactions treated with epinephrine or 2.7% of all reactions). There were no significant differences in age, gender, food challenged, having multiple food allergies, or history of anaphylaxis between those who were treated with epinephrine and those not treated with epinephrine (Table 1). The group receiving epinephrine did not have a higher rate of asthma, but did have a higher rate of previously receiving epinephrine to treat an allergic reaction. Both groups were comparable in terms of food-specific IgE levels, SPTs, as well as median quantity of food protein eliciting the reaction and cumulative dose at termination of food challenge.

The median time between onset of first symptoms and administration of epinephrine was 65 min (range 5–201 min) since the majority of subjects had subjective gastrointestinal symptoms as the initial complaint. Epinephrine was used to treat mild reactions where mild symptoms were observed in multiple body systems or complaints of throat symptoms beyond pruritus were described. For the 2 subjects who were given 2 doses of epinephrine, the second dose was administered 15 and 29 min after the first dose of epinephrine. No subjects required more than 2 doses of epinephrine.

Steroids and intravenous fluids (IVF) were administered more often for reactions treated with epinephrine than for those not treated with epinephrine (Table 2). All subjects were treated with H1 antihistamines. Twenty-three percent received H2 antihistamines, and 2.7% received beta-agonist via nebulization.

Three (4%) subjects had biphasic reactions; recurrence of symptoms developed 55–104 minutes later. All three subjects received steroids as treatment for the biphasic reaction and not the primary reaction.

Subjects were observed for a median of 4 hours prior to discharge (range 3–6 hours). No one was admitted to the hospital, and no delayed symptoms were reported after discharge.

Severity grading

Using the NCI-CTCAE v 4.03 grading system for allergic reactions, [10] the majority of these reactions were categorized as grade 1, mild (63.5%). One third (33.8%) were grade 2, moderate and 2.7% were grade 3, severe. All severe reactions received epinephrine; 75% of moderate reactions and 18.8% of mild reactions were also treated with epinephrine. Of those who received 2 doses of epinephrine, one was characterized as moderate and the other was severe. There was no significant difference in SPT results, sIgE or eliciting dose between severity groups, but those with severe reactions had significantly higher cumulative doses at termination of the food challenges ($p=0.01$). Biphasic reactions occurred in 1 of the severe reactions (50%) and 2 of the moderate reactions (8.3%).

Discussion

Food allergy therapeutic trials are increasing in number and as more therapies are being developed, more screening OFCs will be performed in future larger trials. To our knowledge, this is the first study to assess the rate and the risk factors of food-induced anaphylaxis treated with epinephrine in this population.

The results of this study demonstrate that for diagnostic food challenges used to screen for entry into food therapeutic trials, there is a high rate of reactions requiring epinephrine treatment (39.2%). As per the protocols, some subjects were initially treated with antihistamines for mild symptoms that were not dose-limiting. Epinephrine was subsequently indicated when symptoms persisted or additional symptoms developed. This is a higher rate of epinephrine use than OFCs performed for assessment of clinical tolerance previously reported by our group ($p<0.0001$). [6] In addition, we also report more frequent use of antihistamines and IVF ($p<0.0001$ for antihistamines and $p=0.02$ for IVF), but no difference in steroid or albuterol use. Our rate of treatment with 2 doses of epinephrine (6.9% of the reactions treated with epinephrine or 2.7% of all reactions) was no higher than previous reports for food challenges performed at our institution. [6,7]

The higher severity of these reactions is likely because these challenges were performed for diagnostic purposes in a highly atopic group with one-third having had a history of anaphylaxis and had previously required treatment with epinephrine for allergic reactions. We found that children who received epinephrine during the DBPCFC more often had received epinephrine to treat a previous allergic reaction. Although asthma has been found to be a risk factor for more severe reactions and anaphylaxis, [11,12] we did not see a higher rate of asthma in those who received epinephrine compared to those who did not. In fact, the group not receiving epinephrine had a statistically significantly higher rate of asthma. Similar to the study by Jarvinen, et al, [6] the eliciting and cumulative doses of food allergens were not different between those who received epinephrine and those who did not. We also noted no significant differences in food challenged, SPT wheal size or allergen-specific IgE levels between subjects who received epinephrine and those who did not.

Notably, only about half of these positive reactions had cutaneous symptoms, and often these were not the first signs of allergic reaction. Lower respiratory tract symptoms and cardiovascular symptoms were significantly more frequent for those receiving treatment with epinephrine.

Limitations of the study include the small number of subjects at a single institution. While these subjects were chosen for their high likelihood of reacting to the challenged food, those with a history of life-threatening anaphylaxis, involving hypotension or requiring mechanical ventilation, were excluded.

Of note, all DBPCFCs were performed in the Mount Sinai Clinical Research Unit by our highly experienced research staff. The staff includes RN Clinical Research Coordinators along with RNs and NPs who staff the Clinical Research Unit. They perform multiple OFCs on a daily basis, many for food therapy trials and these DBPCFCs were performed with careful dose escalations as per protocol. Therefore, the high rate of epinephrine use is unlikely to be due to unnecessary use for the treatment of mild reactions. Another strength of this study is that we included both children and adults. All research staff are PALS and/or ACLS certified.

As more novel therapies are being developed for food allergies, growing numbers of individuals with food allergies will be participating in clinical trials and undergoing diagnostic oral food challenges. These results indicate that reactions for screening OFCs tend to be more severe and require more aggressive treatment than OFCs performed to determine if a food allergy has been outgrown. Staff conducting these OFCs must be keenly observant for early symptoms of reactivity and be prepared to treat anaphylaxis. Interestingly, these screening OFCs did not have higher rates of requiring multiple epinephrine doses or biphasic reactions. Therefore, screening OFCs to confirm allergies can be performed safely, but require personnel skilled and experienced in the recognition of early signs and symptoms of anaphylaxis who can promptly initiate treatment.

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Abbreviations

OFC	oral food challenge
FAHF-2	food allergy herbal formula 2

MOIT	milk oral immunotherapy
SPT	skin prick test
DBPCFC	double-blind, placebo-controlled food challenge
IVF	intravenous fluid

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Highlights box**1. 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.

2. 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.

3. How does this study impact current management guidelines?

Diagnostic oral food challenges 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.

Figure 1.

Symptoms of allergic reactions in subjects requiring epinephrine treatment (blue) compared to subjects not requiring epinephrine treatment (red).

Table 1

Patient Characteristics

	Epinephrine n=29 14 yr (7–40 yrs)	No epinephrine n=45 12 yr (7–25 yrs)	P-value
Age, median (range)			0.17
Gender - female (%)	12 (41.4%)	12 (26.7%)	0.21
Food for challenge, n (%)			
Peanut	16 (55.2%)	20 (44.4%)	0.48
Milk	11 (37.9%)	19 (40%)	1
Cashew	1 (3.5%)	0	0.39
Walnut	0	2 (4.4%)	0.52
Sesame	0	4 (8.9%)	0.15
Salmon	0	1 (2.2%)	1
Codfish	1 (3.5%)	0	0.39
Multiple food allergy, n (%)	26 (89.7%)	37 (82.2%)	0.51
History of asthma, n (%)	19 (62.5%)	39 (86.7%)	0.04
History of anaphylaxis, n (%)	11 (37.9%)	15 (33.3%)	0.80
Prior need for epinephrine for allergic reaction, n (%)	14 (48.3%)	11 (24.4%)	0.045
sIgE (kU/L), median (range)	24.4 (0.59 – >100)	32.3 (0.9 – >100)	0.85
SPT (mm wheal), median (range)	8.5 (2–17.5)	8.5 (3.5–16.5)	0.84
Eliciting dose (mg), median (range)	20 (1–496)	10 (1–720)	0.74
Cumulative dose (mg), median (range)	146 (1–2000)	21 (1–2000)	0.23

Table 2

Additional medications given for treatment of positive DBPCFC

	Epinephrine n=29	No epinephrine n=45	P-value
H1 antihistamine, n (%)	29 (100%)	29 (100%)	1
H2 antihistamine, n (%)	8 (27.6%)	9 (20.0%)	0.57
Corticosteroid, n (%)	11 (37.9%)	1 (2.2%)	<0.0001
Intravenous fluid, n (%)	6 (20.7%)	1 (2.2%)	0.01
Albuterol nebulization, n (%)	2 (6.9%)	0	0.15