Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children

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Background: Data about epinephrine use and biphasic reactions in childhood food-induced anaphylaxis during oral food challenges are scarce.
Objective: To determine the prevalence and risk factors of reactions requiring epinephrine and the rate of biphasic reactions during oral food challenges (OFCs) in children.
Methods: Reaction details of positive OFCs in children between 1999 and 2007 were collected by using a computerized database. Selection of patients for OFCs was generally predicated on ≤50% likelihood of a positive challenge and a low likelihood of a severe reaction on the basis of the clinical history, specific IgE levels, and skin prick tests.
Results: A total of 436 of 1273 OFCs resulted in a reaction (34%). Epinephrine was administered in 50 challenges (11% of positive challenges, 3.9% overall) for egg (n = 15, 16% of positive OFCs to egg), milk (n = 14, 12%), peanut (n = 10, 26%), tree nuts (n = 4, 33%), soy (n = 3, 7%), wheat (n = 3, 9%), and fish (n = 1, 9%). Reactions requiring epinephrine occurred in older children (median, 7.9 vs 5.8 years; $P < .001$) and were more often caused by peanuts ($P = .006$) compared with reactions not treated with epinephrine. There was no difference in the sex, prevalence of asthma, history of anaphylaxis, specific IgE level, skin prick tests, or amount of food administered. Two doses of epinephrine were required in 3 of 50 patients (6%) reacting to wheat, cow's milk, and pistachio. There was 1 (2%) biphasic reaction. No reaction resulted in life-threatening respiratory or cardiovascular compromise.
Conclusion: Older age and reactions to peanuts were risk factors for anaphylaxis during oral food challenges. Reactions requiring multiple doses of epinephrine and biphasic reactions were infrequent. (J Allergy Clin Immunol 2009;124:1267-72.)

Key words: *Food allergy, autoinjector, self-injectable, epinephrine, children, anaphylaxis, oral food challenge, food-induced anaphylaxis, peanut allergy, tree nut allergy, cow's milk allergy, milk allergy, egg allergy, allergic reaction*

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.[1] Epinephrine is the drug of choice for the treatment of anaphylaxis.[1-3] Allergic reactions to foods affect as many as 6% of children,[4] and food allergy is the most common cause of anaphylaxis in children (81% of reactions).[5] Children with food-induced anaphylaxis may require more than 1 dose of epinephrine.[6-8] Most information about the rate of multiple doses of epinephrine and biphasic reactions in children comes from reactions occurring in the community. A recent report with a focus on food-related anaphylactic reactions was based on a retrospective chart review of 19 patients (children and adults) who presented to the emergency department; 3 patients (16%), all adults, were administered a second dose of epinephrine.[6] Using a questionnaire, the Anaphylaxis Campaign in the United Kingdom found that a second dose of epinephrine was given in 10% of children with anaphylaxis requiring epinephrine in the community, although details about epinephrine administration were not available (when given, where, by whom, and so forth)[7] Our recent data using a retrospective questionnaire suggested that at least 2 doses of epinephrine were administered in 19% of food-induced anaphylactic reactions occurring in children with food allergy in the community.[8]

Biphasic reactions are those with recurrence of symptoms after resolution of the initial event in 1 to 78 hours.[9] They have been reported in 3% to 20% of anaphylactic reactions in adult and mixed age populations to both oral and parenteral agents.[9] The only study so far that focuses on a pediatric population reports an incidence of biphasic reactions to be 6% in children 1 to 11 years of age retrospectively analyzed from charts of 108 children hospitalized for anaphylaxis.[10] Four reactions were attributed to orally administered antigens (2 antibiotics, fish, and nuts), and 2 were caused by bee stings. In this small population, a delay in epinephrine administration seemed to be associated with a biphasic response. There were differences in the frequency of epinephrine administration, corticosteroid use, or serious cardiovascular or respiratory symptoms between those children experiencing biphasic versus uniphasic reactions. There were no distinguishing signs or symptoms that allowed one to predict whether a biphasic

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Abbreviations used
GCRC: General Clinical Research Center
OFC: Oral food challenge
SPT: Skin prick test

response might occur. We are unaware of pediatric studies that assess the incidence of biphasic reactions to ingested food allergens.

Oral food challenges (OFCs) are the gold standard for initial diagnosis of food allergy.[11,12] Furthermore, they are used in determining when foods can be safely introduced or reintroduced into the diet. Reactive (failed or positive) challenges can elicit skin, respiratory, or gastrointestinal symptoms that may be severe and require medications.[13,14] We are aware of only 1 study that reports the rate of epinephrine administration in failed OFCs (11%), but no risk factors for use of epinephrine, need for multiple doses of epinephrine, or rate of biphasic reactions were reported.[15] We sought to determine the incidence and risk factors of reactions treated with either a single or multiple doses of epinephrine in food-induced anaphylaxis during OFCs in a pediatric population. Furthermore, we assessed the incidence of biphasic reaction in this carefully selected population to serve as an additional resource for clinicians performing food challenges regarding the risks involved with food challenges.

METHODS

Subjects

Review of subjects less than 18 years of age who participated in the OFCs performed for the research purposes in the Mount Sinai General Clinical Research Center (GCRC) between September 2000 and July 2007 was performed by using a computerized database. Children were primarily referred from the Mount Sinai Pediatric Allergy Clinics for OFCs because they had a positive history of reaction to the food in question and/or detectable food-specific IgE. Selection of subjects for OFCs was generally based on the expectation that a child would have $\leq$50% likelihood of a positive challenge on the basis of the food-specific IgE level,[4,16] SPT wheal size,[17] and a lack of history of recent allergic reactions or exposures to known food allergens, but we also considered the age, history, and family preferences.[18] Subjects with a history of severe anaphylaxis (shock, loss of consciousness) in the past 2 years were not challenged. Children who had specific IgE levels or skin tests wheals greater than those that would predict >50% likelihood of a positive challenge were included if they were believed to have a history of recent accidental exposures to a small amount of the food in question without clinical symptoms indicating possible tolerance. Some of the children with the higher food-specific IgE antibody levels were challenged on the basis of the inclusion criteria for a specific research study in which they participated. Details were collected for all positive challenges including age, comorbidities such as asthma, specific IgE levels and SPT results, foods challenged, symptoms, and treatments given. Those with a presentation consistent with food protein–induced enterocolitis syndrome were excluded from further analyses because the management of a food protein–induced enterocolitis syndrome reaction is different than a typical IgE-mediated one, and epinephrine is not used in the treatment. Data were included for individual subjects with positive food challenges to 1 or several foods.

Skin prick test

Skin prick tests (SPTs) were performed with a sterile bifurcated needle (Precision Medical Products, Inc, Denver, Pa) 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 measured at 10 to 15 minutes.

Serum specific IgE measurements

Sera were analyzed for antigen-specific IgE antibody concentration with the ImmunoCAP System (Phadia, Uppsala, Sweden). Results were expressed as kU_A/L of specific IgE antibody.

OFCs

Challenges were performed in the Mount Sinai GCRC, and both single-blind/double-blind, placebo-controlled food challenges and open challenges were included. Blind OFCs were performed as previously described.[13,14] In blind challenges, a maximum of 8 to 10 g dry weight of dehydrated food or equivalent liquid form was camouflaged in a food product (vehicle) and given over a 70-minute period. Seven doses of food were given in progressively larger quantities as follows: 1%, 4%, 10%, 20%, 20%, 25%, and 25%. Subjects received 2 blind challenges per day, 1 placebo and 1 test food. Dietitians in the GCRC prepared the food and randomized the challenges. Negative (asymptomatic) blind OFCs were followed with open feedings within 2 hours. In the open challenges, patients received a meal-size portion for age and were observed for another 2 hours after food consumption. Challenges were stopped at the discretion of the investigators when objective signs and symptoms were observed or subjective symptoms such as throat itching or abdominal pain consistently worsened during the challenge. Medications were administered immediately on detection of an allergic reaction, and administration was based on clinical judgment. Patients were observed for at least 4 hours after an allergic reaction. After discharge, parents were asked to call the research staff in case of late-phase reactions. Biphasic reactions were classified as those with recurrence of symptoms after resolution of the initial event in 1 to 78 hours.[9] Symptoms were considered consistent with anaphylaxis if they occurred rapidly within minutes to several hours after food ingestion and affected at least 2 major organ systems according to the recently established guidelines.[1]

Treatment was prescribed for positive challenges on the basis of the type and severity of reaction according to the guidelines,[1] including epinephrine administered intramuscularly every 10 to 30 minutes or as needed to reverse symptoms and methylprednisone 1 to 2 mg/kg (maximum dose 60 mg) given intravenously for anaphylactic symptoms. Informed consent was obtained from the participants, and the study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, New York, NY.

Statistics

Data were analyzed by using SigmaStat (Version 2.03; SPSS Inc, Chicago Ill). 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, except for multiple comparisons, for which a Bonferroni adjustment was applied.

RESULTS

There were 436 (34%) positive challenges from a total of 1273 challenges (Table I). The most common foods challenged were cow's milk, peanut, hen's egg, and soy, in decreasing order. The children ranged from 1.25 to 18 years, and those with positive challenges were significantly older (median, 6 years) than those with negative challenges (median, 5 years; $P < .001$). Challenges to cow's milk and hen's egg were more commonly positive than the challenges to all other foods combined ($P < .001$ for both), with an especially high rate of positive challenges to egg (74% of all egg challenges). In contrast, OFCs to peanut and foods other than the 9 most common food allergens such as chicken, beef, oat, corn, barley, other meats, fruits, and vegetables were more