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Small percentage of anaphylactic reactions treated with epinephrine during food challenges in Dutch children

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ABSTRACT

Background: Severe allergic reactions, including anaphylaxis, occur during oral food challenges (OFCs) and the first-line treatment of anaphylaxis is epinephrine.
Objective: To evaluate the percentage of anaphylactic reactions treated with epinephrine during OFCs and to identify associated factors for the administration of epinephrine.
Methods: Children who underwent an OFC with peanut, hazelnut, cow's milk, hen's egg, or cashew nut from 2005 through 2015 in the Netherlands were evaluated. Children with reactions meeting the criteria for anaphylaxis according to the European Academy of Allergy and Clinical Immunology guidelines for food allergy and anaphylaxis were included. Children with an anaphylactic reaction treated with vs without epinephrine were compared. Possible factors associated with the administration of epinephrine, such as age, sex, symptoms consistent with asthma, history of an allergic reaction to the tested allergen, and symptom types during the anaphylactic reaction, were evaluated using logistic regression analysis.
Results: Eighty-three children in clinical and research settings (43% boys; median age, 7 years; range, 1–17) who met the criteria for anaphylaxis were included in this study. Thirty-two of 83 children (39%) with anaphylaxis were treated with epinephrine. Respiratory symptoms during the OFC were treated significantly more often with epinephrine than gastrointestinal symptoms ($P = .01$).
Conclusion: Only 39% of children with anaphylaxis, according to the guideline criteria, were treated with epinephrine during the OFC and most of these children had respiratory symptoms. There is need for an easy-to-use international guideline for the treatment of allergic symptoms during OFCs.

Introduction

Oral food challenges (OFCs) are usually required to confirm the diagnosis of food allergy, to evaluate food allergy over time, or to confirm oral tolerance to a tested food. The OFC is considered the reference standard in the diagnosis of food allergy.[1] Literature on the severity of allergic symptoms during OFCs describes prevalence in the range of 20% to 50% for anaphylactic reactions.[2,3] Currently, anaphylaxis is a clinical diagnosis often based on criteria of the European Academy of Allergy and Clinical Immunology (EAACI) guidelines for food allergy and anaphylaxis[4] (Table 1). The first-line treatment of anaphylaxis is epinephrine.[5] However, the actual use of epinephrine for the treatment of anaphylaxis during OFCs is poorly described and numbers are unknown. Furthermore, the guidelines were not specifically developed for the use of epinephrine during OFCs. The primary aim of this study was to evaluate the percentage of anaphylactic reactions treated with epinephrine during OFCs and to identify factors associated with the administration of epinephrine.

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Table 1
Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:	
1	Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (eg, generalized hives; pruritus or flushing; swollen lips, tongue, or uvula) and *≥1 of the following:*
a	Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, decreased PEF, hypoxemia)
b	Decreased BP and associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2	≥2 of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a	Involvement of skin and mucosal tissue (eg, generalized hives, itch or flush, swollen lips, tongue, or uvula)
b	Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, decreased PEF, hypoxemia)
c	Decreased BP with associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d	Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3	Decreased BP after exposure to known allergen for that patient (minutes to several hours)
a	Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP[a]
b	Adults: systolic BP <90 mm Hg or >30% decrease from that person's baseline

Abbreviations: BP, blood pressure; PEF, peak expiratory flow.
[a]Low systolic BP for children is defined as lower than 70 mm Hg at 1 month to 1 year, lower than 70 mm Hg + (2 × age) at 1 to 10 years, and lower than 90 mm Hg at 11 to 17 years.

Methods

Study Design and Subject Selection

This retrospective study evaluated open and double-blinded placebo-controlled (DBPC) OFCs with peanut, hazelnut, cow's milk, hen's egg, or cashew nut performed in children 0 to 18 years old from 2005 through 2015 at 3 tertiary care centers in the Netherlands. The OFCs were performed in a clinical setting (C-group; open and DBPC OFCs) and a research setting (R-group; DBPC OFCs; IDEAL cashew nut study, collaboration of 3 tertiary care centers for food allergy, trial number NTR3572).[6] Children with an anaphylactic reaction during the OFC were included. Criteria of the EAACI guidelines were used to define anaphylaxis[4] (Table 1). Information on age, sex, skin prick test results of tested allergens, asthma, history of allergic reaction, type and severity of reaction during the OFCs, time from exposure to reaction, and the amount of allergen causing the reaction were collected in a database.

Oral Food Challenge

All children underwent an OFC with peanut, hazelnut, cow's milk, hen's egg, or cashew nut. The tested allergen was administered in increasing amounts at a maximum of 7 doses at 30-minute intervals. The OFC material was standardized and validated[7] and the amount of allergen per dose increased semi-logarithmically. The first step consisted of 1 mg of food protein, followed by increasing doses of 3, 10, 30, 100, 300, and 1,000 mg. In the R-group, the children received an extra dose (dose 8) containing 1,736 mg of cashew nut protein. In the present study, a failed OFC was considered a positive result (ie, allergy confirmed) when (1) objective symptoms occurred, (2) when subjective symptoms reoccurred twice after the same dose of OFC material had been administered (ie, symptoms occurring on 3 consecutive administrations of the same dose),[8] or (3) severe subjective symptoms persisted for longer than 1 hour. Children with an anaphylactic reaction during the OFC received a prescription for an epinephrine auto-injector with extensive instructions for use.

Statistical Analysis

The patient and study characteristics were reported as median, range, and proportion. Children with an anaphylactic reaction treated with epinephrine were compared with children with an anaphylactic reaction not treated with epinephrine. Potential influencing factors associated with the administration of epinephrine during an anaphylactic reaction, such as age, sex, symptoms consistent with asthma, history of an allergic reaction to the tested allergen, symptom types during the anaphylactic reaction, open OFCs vs DBPC OFCs, the individual challenged food, having 1 vs multiple food allergies, eczema, rhinoconjunctivitis, and previous anaphylactic reaction, were investigated with multivariable logistic regression analysis. Characteristics of children from the C-group and R-group were compared using χ^2 test, Mann-Whitney *U* test, and univariate logistic regression. *P* values less than .05 were considered statistically significant. Statistical analyses were done using SPSS Statistics 21 (IBM Corp, Armonk, New York).

Results

Study Population

In total, 312 of 900 (35%) OFC reactions (714 [79%] in the C-group and 186 [21%] in the R-group) with peanut, hazelnut, cow's milk, hen's egg, or cashew nut were assessed as positive (175 of 714 in the C-group [25%]; 137 of 186 in the R-group [74%]). Of the 175 positive OFC reactions in the C-group, 34 children (19%) met the criteria for anaphylaxis; of the 137 positive OFC reactions in the R-group, 49 children (36%) met the criteria for anaphylaxis. Eighty-three children (43% boys; median age, 7 years; range, 1–17 years) were included in this study. For the C-group and R-group combined, 32 of 83 children (39%) with an anaphylactic reaction received epinephrine during the OFC (Table 2). Two children in the R-group and 6 children in the C-group received epinephrine

Table 2
Number of Patients Treated With Epinephrine With and Without Anaphylaxis in the Clinical and Research Groups

	Positive challenge reactions	Anaphylaxis		No anaphylaxis	
	312	83 (27%)		229 (73%)	
		Epinephrine	No epinephrine	Epinephrine	No epinephrine
Clinical group	175	24	10	6	135
Peanut	74	11 (15%)	4 (5%)	3 (4%)	56 (76%)
Hazelnut	26	3 (12%)	1 (4%)	1 (4%)	21 (81%)
Milk	30	4 (13%)	2 (7%)	1 (3%)	23 (77%)
Egg	45	6 (13%)	3 (7%)	1 (2%)	35 (78%)
Research group	137	8	41	2	86
Cashew	137	8 (6%)	41 (30%)	2 (1%)	86 (63%)
Total epinephrine		32 (39%)		8 (3%)	