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Epinephrine autoinjector prescription in food-allergic adults: symptom-based only or allergen-based also? An italian multi-centre study

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Key words

Food allergy, epinephrine, anaphylaxis

Summary

Background: *Epinephrine is the treatment of choice for acute food-allergic reactions but existing guidelines state that it should be prescribed uniquely to patients who already experienced at least one food-induced anaphylactic episode.* ***Objective:*** *We investigated whether in Italy epinephrine auto-injector is prescribed uniquely following the existing guidelines only, or is allergen-informed as well (i.e., based on the potential risk associated with sensitization to certain food allergens), and hence preventive.* ***Methods:*** *1110 adult patients (mean age 31 years; M/F 391/719) with food allergy seen at 19 allergy outpatient clinics were studied. Patients with a history of probable anaphylaxis were identified. Subjects were classified as having primary (type 1) and/or secondary (type 2) food allergy and were divided into several subgroups based on the offending allergen/food. Epinephrine prescriptions were recorded and analyzed both as a whole and by sensitizing allergen.* ***Results:*** *Epinephrine was prescribed to 138/1100 (13%) patients with a significant difference between subjects with type-1 and type-2 food allergy (132/522 [25%] vs 6/629 [1%]; p< 0.001). The epinephrine group included most patients with a history of anaphylaxis (55/62 [89%]) or emergency department visits 106/138 (77%). In some specific subsets, namely fish-, tree nuts-, and lipid trasfer protein (LTP)-allergic patients, epinephrine was prescribed to*

patients without a history of systemic allergic reactions. ***Conclusions****: Italian allergy specialists prescribe epinephrine auto-injectors both on the basis of clinical history of severe reactions and on a critical analysis of the hazard associated with the relevant protein allergens, which suggests a good knowledge of allergens as well as acquaintance with the guidelines for prescription of emergency medication.*

Introduction

Foods are unquestionably one of the main causes of anaphylaxis worldwide (1). As a rule, unless there is sensitivity to labile plant food allergens, food-allergic patients are recommended the strict avoidance of the ingestion of potentially offending food(s). However, allergen avoidance is often difficult due to several reasons. Some allergen proteins are widespread and cross-reacting, which poses the patient at risk of allergic reactions following the ingestion of foods that are completely different from the offending one and hence considered harmless. Further, contamination of safe foods may occur by the use of kitchen utensils both at home and at public places such as restaurants or bars (2). Finally, the presence of a certain food is not always clearly specified on product labels or on restaurant menus. All these situations pose a considerable risk of accidental exposure to the offending allergen (3).

Epinephrine administration remains the milestone of treatment of acute allergic reactions (4), and food-allergic individuals at risk of anaphylactic reactions should be always prescribed an epinephrine auto-injector and given proper instructions about its correct use (5). These patients should always carry the device since it has been shown that allergic reactions may occur at sites considered as safe such as home, school, workplaces, and hospitals (6).

Data about the implementation of existing guidelines about epinephrine prescription in peripheral non-academic outpatients clinics are very few in medical literature. A recent study performed in the Netherlands showed that prescription of emergency medication did not fully reflect the potential severity of adverse reactions in patients allergic to plant-derived foods (7).

In Italy, during the last 2 years, epinephrine auto-injector has become free of cost for allergic patients and completely reimbursed by the NHS if the drug is prescribed by specialist allergologists working in public hospitals and outpatient clinics on the basis of a defined diagnosis of food allergy. This implies that epinephrine should be prescribed uniquely to food-allergic patients who already experienced at least one anaphylactic episode but not to subjects sensitized to potentially harmful allergens reporting reactions other than anaphylaxis, or without a clinical history of adverse reactions to foods. In other words, the Italian NHS presently guarantees a preventive treatment uniquely in a proportion of the population potentially at risk. The present study aimed to investigate in a multi-center survey whether epinephrine auto-injector prescription in Italy follows the existing guidelines only (i.e. if only patients with a history of food-induced anaphylaxis are prescribed the drug) or it is also allergen-informed preventive (i.e. based on a risk assessment depending on the chemical/physical characteristics of sensitizing allergens).

Patients and methods

Patients

1110 (4%) patients older than 12 years (mean age 31 years [range 12-79]; M/F 391/719] diagnosed as having IgE-mediated food allergy out of 25813 subjects first visited at 19 allergy outpatient clinics scattered throughout Italy from January 1st to December 31st, 2007 were included in this study.

Food allergy was diagnosed only in the presence of an unequivocal history of adverse reactions occurring some minutes up to 2 hours after the ingestion of the offending food(s) confirmed by a clear-cut positive SPT and/or by elevated circulating food-specific IgE. Clinical symptoms suggesting food allergy included oral allergy syndrome (defined as the rapid onset of itching of the oral mucosa with or without angioedema of lips and tongue)(8), acute generalized urticaria with or without angioedema (9), and/or anaphylaxis (10).

Definition of anaphylaxis

The doctors of participating centres reviewed the medical recordings of patients reporting suspect anaphylaxis. Following previously published clinical criteria (11) an ana-

phylactic reaction was considered highly likely when any of the following 3 criteria were fulfilled:

1. Acute onset of an illness involving skin, mucosal tissue, or both plus at least 1 of the following: a) respiratory compromise; b) reduced blood pressure or associated symptoms of end-organ dysfunction (collapse, syncope, incontinence).
2. Rapid onset after exposure to a likely allergen for that patient of 2 or more of the following: a) Involvement of skin or mucosal tissue; b) respiratory compromise; c) reduced BP or associated symptoms; d) persistent gastrointestinal symptoms.
3. Systolic BP < 90 mmHg or > 30% decrease from baseline BP after the ingestion of a known allergen for that patient.

In-vivo and in-vitro tests

Hypersensitivity to food allergens was detected by commercial food extracts (ALK-Abello, Spain). The series tested in all patients with suspect food allergy in all participating centres included egg white, egg yolk, cow's milk, shrimp, codfish, wheat, maize, soybean, peanut, sunflower seed, bean, walnut, hazelnut, tomato, carrot, orange, peach, celery, almond, sesame seed, kiwi, and banana.

In the case of suspect allergy to foods not included into this series, commercial extracts from the same or other companies (where available) and/or fresh foods were used for skin testing. Anisakis simplex SPT (ALK-Abello) was tested in patients reporting systemic allergic symptoms following the ingestion of raw or underdone fish and scoring negative on SPT with fish extract. Fresh foods were tested by the prick-prick technique. All SPT were carried out on the volar side of the forearm using disposable prick lancets (ALK-Abello). SPT with saline and histamine 10 mg/ml were used as negative and positive control, respectively. Readings were taken at 15 minutes; wheals with a mean diameter > 3 mm were considered positive (12).

In some centres hypersensitivity was confirmed also by specific IgE measurements (Uni-CAP, Phadia Sweden). In these cases specific IgE levels > 0.35 kU/l were regarded as positive.

Although a recent study on patients sensitised to stable food allergens, namely lipid transfer protein, showed that double-blind, placebo-controlled food challenges (DBPCFC) can be carried out quite safely (13), in view of the severity of reported allergic reactions and of the limited acquaintance of many of the participants with oral food challenges, due to the fear of possibly severe adverse reactions, diagnosis of food-induced anaphylaxis was not confirmed by DBPCFC.

Classification of patients sensitised to plant food allergens

In view of the extremely large variety of plant-derived foods possibly involved in allergic reactions, in order to uniform the recording of clinical data by participating centres, patients with plant-food allergy were distinguished in two main groups:

1. Type 1 (Primary) food allergy. This category included the following subgroups of patients with primary sensitisation to plant-derived foods.

a) Lipid transfer protein (LTP). This group included all patients allergic to LTP irrespective of the offending food(s). LTP hypersensitivity was diagnosed in the presence of a positive SPT with commercial peach extract (ALK-Abello, Spain). Previous studies showed that this peach extract virtually contains only LTP at a concentration of 30 μg/ml, and that a positive SPT with this extract may be used as a clinical marker of sensitization to this protein (14, 15) with only minor exceptions (16). Offending foods for LTP-allergic patients included all *Rosaceae* (apple, pear, peach, cherry, plum, apricot, medlar, almond, strawberry), tree nuts, maize, rice, beer, and grapes (17).

b) Tree nuts. This group included all patients allergic to tree nuts (including hazelnut, walnut, Brazil nut, pine nut, almond, pistachio, chestnut, and cashew) but not to LTP. Diagnosis was based on a positive SPT with commercial extract (when available) or with fresh offending nut in the absence of skin reactivity to both commercial peach extract and birch pollen extract. Previous studies showed that commercial walnut extract contains only stable allergens and can therefore be used as a means to rule out sensitisation to labile allergens homologous to pollen proteins (15).

c) Seeds. Patients allergic to one or more seeds (such as sesame, sunflower, poppy, or other seeds) but not sensitised to tree nuts were included in this group.

d) Legumes. This group included subjects allergic to one or more legumes including peanut, bean, string bean, pea, chickpea, lupine, and lentil.

e) Cereals: This subgroup included patients with clinical allergy to cereals (wheat, barley, maize, rice, rye) not sensitised to LTP, as shown by negative SPT with commercial peach extract.

f) Kiwi: this category included subjects with single kiwi allergy.
g) Allergy to single vegetable foods. This category included all remaining plant-derived foods that caused isolated allergic reactions in single individuals in the absence of birch pollen hypersensitivity.

Type 2 (Secondary) food allergy:
This category included patients with plant-food allergy caused by cross-reactivity to a primary sensitizer, and included the following subgroups:
a) Pollen-food allergy syndrome: This subgroup included patients either mono-sensitised to birch pollen (Bet v 1) or showing sensitization to all seasonal airborne allergens (and, hence possibly sensitised to Profilin). Since both Bet v 1-homologous proteins and profilin are heat- and pepsin-labile allergens, a pollen-food allergy syndrome was diagnosed if patients reported good tolerance of the offending foods if these were cooked or otherwise processed, and/or in the presence of positive SPT with fresh offending foods but negative SPT with commercial extract of the same foods.
b) Latex-fruit allergy syndrome. Patients primarily sensitised to natural rubber latex with a history of allergy to foods known as being potentially cross-reacting, such as chestnut, avocado, kiwi, papaya, and banana.
c) Mugwort-celery- spice syndrome. Patients primarily sensitised to mugwort with a history of allergy to potentially cross-reacting vegetable such as celery, fennel, anise, bell pepper, and other spices.

Patients sensitised to non-plant foods were grouped by allergen. For instance, patients allergic to shrimp, squid, octopus or shellfish were considered as possibly sensitised to tropomyosin and grouped together (group "shrimp"); similarly, those allergic to different fishes were grouped together, as were those allergic to different meats, and so on.

Study approval and informed consent

Since this observational study was carried out on patients spontaneously presenting at the different centres for routine evaluation and epinephrine was prescribed based uniquely on the basis of doctors' experience, no institutional review board was needed. As all other subjects attending allergy clinics in Italy, study patients gave an informed oral consent to the use of their data in an anonymous form for study purposes.

Statistics

Proportions were compared by chi-square test with Yates' correction. Means were compared by two-tailed Student's t-test. Probability levels < 5% were considered statistically significant.

Results

The overall prevalence and the clinical features of the different types of food allergy, along with the rate of epinephrine auto-injector prescription, are shown in table 1. A total of 522 patients had a type-1 food allergy; in these patients fruits and vegetables represented by far the most frequently offending foods (393/522; 75%). Among animal-derived foods, shrimp was the most frequently offender. Notably, the large majority of patients with type 1 food allergy had a clinical history of systemic symptoms following exposure to offending food, the only exception being kiwi, which induced local symptoms in a majority of cases.
Type-2 food allergy was diagnosed in 629 cases. The pollen-food allergy syndrome represented the most frequent type-2 food allergy (98% of cases), whereas both the latex-fruit allergy syndrome and the mugwort-celery-spice syndrome were very uncommon. The large majority of those with pollen-food allergy syndrome had only mild local symptoms and reported systemic symptoms only in a very little proportion of cases (3%), whereas both the latex-fruit allergy syndrome and the mugwort-celery-spice syndrome were frequently associated with systemic symptoms.
Fifty-one patients showed a type 1 + 2 food allergy due to co-sensitization to pollen related food allergens and to primary food allergens (plant-derived foods in most cases) following the criteria adopted in this study. Not surprisingly, most of these cases were observed in the northern part of the country where birch pollen allergy is rather common. These subjects were analyzed as they had a primary (type-1) food allergy only.
Epinephrine auto-injectors were prescribed to 138/1100 (13%) patients (M/F 55/83; mean age 31.4 years, range 12-72 years) with a statistically significant difference between subjects with type 1 and type 2 food allergy (132/522 [25%] vs 6/629 [1%], respectively; p< 0.001). The epinephrine group included the large majority of patients with a history of food-induced anaphylaxis (55/62 [89%], Table 1). The 7 subjects that were not prescribed epinephrine despite a clinical history of anaphylaxis in-

Table 1 - Offending foods, prevalence of systemic reactions (other than anaphylaxis) and of anaphylaxis, and rate of epinephrine auto-injector prescription in 1110 food-allergic Italian adults

		Clinical history		Auto-injector prescription			Prescriptions	
Allergen	No.	U/A	Anaphylaxis	Total	Anaphylaxis	ER	Missing	Exceeding
Fish	22	18 (82%)	1 (5%)	6 (27%)	1	2	0	4
Shrimp	68	61 (90%)	10 (15%)	14 (31%)	8	14	2	0
Milk	13	9 (69%)	1 (8%)	4 (31%)	1	2	0	2
Egg	17	13 (76%)	1 (6%)	2 (12%)	1	1	0	1
Meat	4	3 (75%)	1 (25%)	1 (25%)	1	1	0	0
Snail	2	2 (100%)	0	0 (0%)			0	0
Anisakis	3	3 (100%)	1 (33%)	1 (33%)	1	1	0	0
Wheat	11	8 (73%)	3 (27%)	7 (64%)	3	6	0	1
LTP (incl. Rosaceae, nuts, maize, etc).	216	130 (60%)	19 (9%)	45 (21%)	19	32	0	13
Sesame/sunflower seed	6	6 (100%)	2 (33%)	4 (67%)	2	3	0	1
Peanut	19	16 (84%)	1 (5%)	5 (26%)	1	4	0	1
Tree nuts	65	52 (80%)	9 (14%)	25 (38%)	9	19	0	6
Kiwi	23	7 (30%)	0	0 (0%)			0	0
Brazil Nut	1	1 (100%)	1 (100%)	1 (100%)	1	1	0	0
Soybean	9	5 (56%)	0	0 (0%)			0	0
Legumes	9	7 (78%)	4 (44%)	5 (55%)	2	5	2	0
Pineapple	3	2 (67%)	0	0 (0%)			0	0
Avocado	1	1 (100%)	1 (100%)	1 (100%)	1	1	0	0
Pine nut	12	10 (84%)	0	4 (33%)		4	0	0
Fig	1	1 (100%)	0	1 (100%)			0	1
Eggplant	2	0 (0%)	0	0 (0%)			0	0
Buckwheat	4	3 (75%)	1 (25%)	1 (25%)	1	1	0	0
Spinach	2	2 (100%)	1 (50%)	1 (50%)	1	1	0	0
Mango	1	1 (100%)	0	0 (0%)			0	0
Boletus mushroom	1	0 (0%)	0	0 (0%)			0	0
Tomato	2	1 (50%)	1 (50%)	2 (100%)	1	2	0	0
Watermelon	3	1 (33%)	0	2 (66%)	0	1	0	1
Fennel	1	0 (0%)	0	0 (0%)			0	0
Garlic	1	0 (0%)	0	0 (0%)			0	0
Type 2 food allergies	629	39 (6%)	4 (<1 %)	6 (1%)	1	5	3	1

U/A: urticaria with or without angioedema

Missing prescriptions: Patients with a clinical history of anaphylaxis that were not prescribed epinephrine.

Exceeding prescriptions: Patients without a history of anaphylaxis or ER assistance that were prescribed epinephrine.

Type 2 food allergies include subjects with pollen food allergy syndrome, latex-fruit allergy syndrome, and mugwort-celery spice syndrome.

The last 3 columns show the number of patients prescribed epinephrine (column 4), and how many of those prescribed epinephrine had a clinical history of anaphylaxis (column 5) and/or a history of Emergency Department visits (column 6).

cluded 2 shrimp-allergic patients, 2 subjects allergic to legumes, and 3 patients with type-2 food allergy (Table 1). The rate of epinephrine prescription in patients with a history of anaphylaxis differed significantly between patients with type-1 or type-2 food allergy (54/58 [93%] vs 1/4 [25%]; $p < 0.001$).

The analysis of data showed that another main criterion adopted by participating doctors to prescribe epinephrine was a history of emergency department visit due to food-induced systemic reactions (including anaphylaxis or urticaria/angioedema with or without respiratory symptoms). In fact, 106/138 (77%) subjects who were pre-

scribed epinephrine auto-injector had sought for care at the ER (Table 1). Interestingly, in this case no difference between patients with type-1 or type-2 food allergy was observed (101/132 [77%] vs 5/6 [83%], respectively; p= NS).

Within the different subgroups with type-1 food allergy including > 5 individuals, epinephrine prescriptions ranged between 12% (egg) and 67% (sesame seed, sunflower seed) with most frequent prescriptions occurring in patients allergic to wheat or legumes (table 1). Interestingly, although patients were mostly prescribed epinephrine in the light of a clinical history of anaphylaxis and/or emergency department visits, in some specific subsets epinephrine prescriptions in excess (i.e., in subject without a history of severe allergic reactions) were observed. This was particularly common in patients allergic to fish (4/6 [67%] prescriptions in excess), to tree nuts (6/25 [24%]), and especially to LTP (13/45 [29%]).

In patients with type 2 food allergy epinephrine was rarely prescribed (4/629; < 1%); of 6 patients prescribed the drug, 1 had a mugwort-celery-spice syndrome, 1 a latex-fruit-allergy syndrome, and 4 a pollen-food allergy syndrome. In 5 cases prescriptions followed an emergency department visit, although 3/4 patients diagnosed as having had an anaphylactic episode were not prescribed epinephrine (Table 1).

Discussion

Although several surveys of epinephrine prescription appeared recently in the medical literature (18-20), this is probably one of the first studies analysing epinephrine auto-injector prescription in food allergy not only as a whole, but also by sensitising allergen. The virtual lack of peanut allergy in Italy (21), which represents the major cause of fatal or near-fatal anaphylaxis in Anglo-Saxon as well as in some European and Asian countries (4,7,20,22), clearly produces a change in the epinephrine prescription patterns and leads to consider other subsets of food-allergic patients. In this sense, allergy to lipid transfer protein, which is the most relevant cause of primary food allergy in Italy (21), as well as the main cause of food-induced anaphylaxis (23), represents an interesting model. Only about 20% of LTP–allergic patients were prescribed epinephrine auto injector, a proportion that is inferior to that of patients with other types of food allergy. However, LTP-allergic patients may experience an array of clinical conditions ranging from a life-lasting oral allergy syndrome to anaphylaxis, and this is the most likely reason why the majority of patients sensitised to this allergen were not prescribed epinephrine. In this subgroup most prescriptions were symptom-based (i.e., based on a history of severe clinical symptoms, as suggested by the emergency department visits). However, interestingly, in about 30% of cases epinephrine prescriptions were allergen-based (i.e., patients were prescribed auto-injectors because they were sensitised to a potentially harmful allergen, although the did not yet experience any severe allergic reaction). A similar trend was observed in patients sensitised to foods that are more frequently associated with systemic reactions, such as milk, wheat, shrimp, seeds, tree nuts, peanut, and fish. In these subgroups, along with an overall high (symptom-based) rate of epinephrine prescription, a proportion of patients were prescribed epinephrine auto-injectors with an exclusively preventive intent. This might depend on the fact that this study was based on specialized allergy clinics where doctors are acquainted with the guidelines for prescription of emergency medication and show a good knowledge of the chemical/physical characteristics of the various allergen proteins and, consequently, a higher consciousness of the potential risks associated with sensitisation to certain foods (24).

By comparing this study with a similar Dutch survey (7), it appears that in the Netherlands epinephrine prescriptions were on the whole limited and seemingly biased by the impact of food allergy on patient's quality of life, which is negative for patients and unrelated to both the allergen involved and the severity of the allergic reaction. The present Italian survey seems to reveal a more careful and critical analysis of the potential role of allergen proteins involved in allergic reactions by participating doctors and, hence, an improved appropriateness of the prescription of epinephrine.

In fact, the rates of symptom-based epinephrine prescriptions in patients with type-1 and type-2 food allergy were very similar, which is in keeping with studies showing that even allergens involved in pollen-food allergy syndrome, and hence presumptively pepsin-sensitive, may in some cases induce severe reactions (25).

In conclusion, this study shows that, along with the obvious symptom-based epinephrine prescription (as recommended by most guidelines as well as by Italian national drug regulatory organisms) a new, allergen-based, trend in epinephrine prescription is slowly emerging. This type of prescription is not based on clinical history but on the potential harmfulness of sensitizing allergen, and hence

points to prevent severe allergic reactions in sensitized patients that did not experience systemic reactions yet. It is possible that such way of prescribing will grow-up as far as an increasing number of recombinant allergen proteins, including many food allergens, are becoming available for in-vitro diagnosis of allergic diseases leading to a more refined component-resolved diagnosis and to a better definition of the pathogenic role of the various allergen proteins (26). In this sense the allergy specialist remains the only professional able to integrate clinical experience and knowledge of the characteristics of the allergens.

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