

Skin prick tests and in vitro immunoassays with native spices and spice extracts

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Background: Skin prick tests of native spices (commercial powdered spices) are common in patients with allergy to birch or mugwort pollen. Clinical symptoms from spices are infrequent but occasionally severe.

Objective: To compare the skin prick test results with native spices and spice extracts and to determine the clinical relevance of test material.

Methods: Skin prick tests with the native spices coriander, caraway, paprika, cayenne, mustard, and white pepper were made twice at 2-month to 2.9-year intervals in 49 patients. During the latter time, tests were also made with spice extracts and spice-specific serum IgE was measured.

Results: The reproducibility of skin test results with native spices was 67% to 100%. Spice extracts, except white pepper, elicited positive skin test reactions in half those with positive reactions to native spices. Higher specific IgE concentrations (≥ 3.5 PRU/mL) were seen in cases where the skin tests were positive to the corresponding spices with 5% extracts of >8 kD Mw. Three-fourths of the patients with positive skin tests to native spices were positive to birch pollen and one-half to a vegetable. Mild clinical symptoms from spices were reported by one-third.

Conclusions: Spice allergens partly crossreact with those of pollens and vegetables. A minority of spice allergens may give clinical symptoms. The >8 -kD 5% extracts may be relevant skin prick test materials for identifying patients at risk of developing severe symptoms from ingested spices.

INTRODUCTION

In a previous study of 1,500 patients, native spices (eg, mustard, coriander, caraway, paprika, and cayenne) produced positive scratch test reactions almost exclusively in atopic patients, especially in those with birch pollen allergy.¹ Some authors have reported positive skin prick tests and specific IgE to spices, especially those from the Apiaceae family, more frequently in patients with allergy to mugwort pollen and celery (a "celery-mugwort-spice syn-

drome")²⁻⁸; among whom caraway, fennel, parsley, and paprika have most often produced clinical symptoms.^{2,3} Ingested mustard has caused anaphylaxis⁹⁻¹³ as has coriander,¹⁴ while well-documented IgE-mediated asthma from spice dust has also been reported.¹⁵

Skin prick tests with dialyzed, lyophilized, nonreconstituted spice extracts (cutoff 3.5 kD) elicited equal or stronger reactions than native spices when the tests were performed by mixing approximately 2 mg dry material with a drop (50 μ L) of saline on the skin prior to piercing, but 5% (wt/vol)-reconstituted extracts elicited weaker or negative results.¹⁶

Since 1980, native spices have been included in our skin prick test food series. Although positive skin prick test and in vitro immunoassay results from spices are common, clinical symptoms are fairly rare but may be severe. This discrepancy between the skin tests and patient symptoms

suggested a need for acquiring better test allergens.

In the present study we made repeated skin prick tests with native spices and with two types of spice extracts, and compared them with in vitro immunoassay results and clinical symptoms. High spice-specific IgE values were encountered in patients reacting to spice extracts in the skin prick tests. Clinical symptoms from the ingestion of spices were reported by one-third the patients, but the symptoms did not correlate with the results of skin prick tests or in vitro immunoassay results.

MATERIALS AND METHODS

Patients

During January 1, 1988 to September 30, 1990, skin prick tests with two or more native spices were performed in 922 patients. Mustard and white pepper were tested in all 922 patients and coriander, caraway, paprika, and cayenne in 461. Of these 922 patients 117 (13%) developed positive results from one or more spices, while 49 (5%) showed strongly positive results (diameter of the wheal ≥ 5 mm) and were invited for reinvestigation 2 months to 2.9 years (mean 1.6 years) later. Of the latter, 23 were males and 26 females, aged 1 to 51 years (mean 16.5 years); half were <15 and one-fourth <5 years of age. Of the patients 28 had atopic dermatitis with respiratory symptoms (two of whom also had recurrent gastric pain), 12 had respiratory symptoms without eczematous dermatitis (two of whom also had urticarial episodes and one hoarseness), eight had atopic dermatitis with no other atopic symptoms and one had chronic hand eczema without contact allergies. This last patient had no history of atopic flexural dermatitis or

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allergic respiratory symptoms although she reacted to cat epithelium by skin prick testing.

Test Materials

The following native spices (commercial powdered spices) were used for the skin prick tests in 1988–1990: mustard (including seeds of *Sinapis alba* and *Brassica nigra*), coriander, caraway, paprika, cayenne, and white pepper. For the reinvestigation, the native spices were supplied by Laboratorium Diephuis, Groningen, The Netherlands (from a local wholesale store in Groningen), and by the kitchen of University Hospital, Oulu. The spice extracts for the reinvestigation were made by Laboratorium Diephuis.

The spice extracts were made as follows. Powdered native spices from the local wholesale store in Groningen were mixed 1:10 with sodium bicarbonate solution (9 g sodium chloride, 1 g sodium bicarbonate, and 5 g of phenol in 1L purified water), pH 7.2, and kept in a refrigerator overnight. The mixture was then centrifuged at 14,000 rpm for 30 minutes and filtered through a 0.2- μ m membrane. The extract was then dialyzed against distilled water at 4 to 8 °C in a Spectra/Por dialyzing tube with a molecular cutoff at 1 kD or 8 kD. The water was replaced on three consecutive days with three replacements/day until the conductivity fell to <200 μ S. The conductivity was measured with a Consort K220 conductivity meter with an electrode equipped for temperature compensation. After dialysis, the extract was passed again through a 0.2- μ m membrane filter and the dialyzed extracts then lyophilized and reconstituted in a 1:1 water-glycerine mixture with sodium chloride (0.25 g/mL) and sodium bicarbonate (0.125 g/mL) to obtain 1:10, 1:20, and 1:100 wt/vol test materials. The final test materials were then sterilized by passing through a sterile Gelman Acrodisk 0.2- μ m membrane filter and put into sterile 5-mL vials.

The pollen test materials were commercial 10-histamine equivalent prick

test solutions from ALK, Hørsholm, Denmark. The following fresh fruits and vegetables were tested: potato, carrot, apple, swede (Swedish turnip or rutabaga), and celeriac (celery root).

Skin Tests

Pollens and spice extracts were tested according to the recommendations of the Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology¹⁷ using a prick test lancet with 1-mm tip (Prick-Lancett, Ewo Care AB, Gislaved, Sweden). Native spices were tested by first mixing approximately 4 mg powdered spice and 50 μ L saline on the skin, and then pricking into the skin. Fruits and vegetables were tested by the prick-prick-method in which the flesh of fruits or vegetables was first pricked with the lancet, which was thereafter used to prick the skin.^{17,18} Histamine dihydrochloride 10 mg/mL was used as the positive control. 1:1 glycerosaline was used as the negative control for pollens and spice extracts, and saline for native spices and fresh fruits/vegetables. The reactions were read according to the guidelines of the Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology¹⁷ and were regarded as positive if they were half the sizes produced by the histamine minus saline controls, and at least 3 mm in diameter.

Total and Specific IgE (RAST)

Total IgE was measured with the QuantiCLONE Total IgE Kit (Kallesstad Diagnostics, Inc., Chaska, MN, USA). Specific IgE for mustard, caraway, and paprika was measured using the Phadebas RAST method (Pharmacia, Uppsala, Sweden). Allergen-specific IgE for coriander and cayenne, and in some cases also for mustard, caraway, and paprika, was measured by one of the authors (S M-K) as follows: 10 mg powdered spices from each Laboratorium Diephuis' batch, which were also used in the second skin test, were mixed with 1 mL phosphate buffer (100 mM, pH 7.4) and allowed to remain for 90 minutes at

room temperature. The mixture was then centrifuged at 3,350 g for ten minutes and 100 μ L supernatant were covalently coupled to cyanogen bromide-activated paper discs.¹⁹ The coupling protein concentration/disc was 156 μ g for mustard, 22 μ g for paprika, 107 μ g for caraway, and 25 μ g for coriander and cayenne. The results were calculated from a standard birch IgE curve supplied with the Phadebas RAST kit and expressed as PRU/mL. Specific IgE values ≥ 0.35 PRU/mL were regarded as positive.

Statistical Methods

Pearson's correlation coefficient was used for the analysis of the cross-reactions between the skin test reactions to native spices and fresh fruits and vegetables. The reactions were taken as positive or negative, but the diameter of the reaction wheel was not otherwise considered.

RESULTS

Skin Prick Test Results with Native Spices and Spice Extracts

During the first test, all 49 patients were tested with native mustard and white pepper and 29 also with coriander, caraway, paprika, and cayenne. During the retest, patients were tested with those native spices that had produced positive results in the first skin test. Of the 49 patients with positive skin prick tests to spices in the first test, 46 also showed positive results to native spices in the second test (Fig 1). The reactions in the second test were mostly smaller than in the first test. There were also differences between the reactions of the two parallel tests (with native spices supplied by Laboratorium Diephuis and those from our hospital kitchen) done at the second test time. Their sizes showed differences up to 9 mm, which even influenced the mean sizes of the test reactions (Fig 1).

Skin prick tests with extracts were performed on patients reacting positively in the second test to the native spices from Laboratorium Diephuis. The 1-kD and the 8-kD extracts gave positive skin prick test reactions

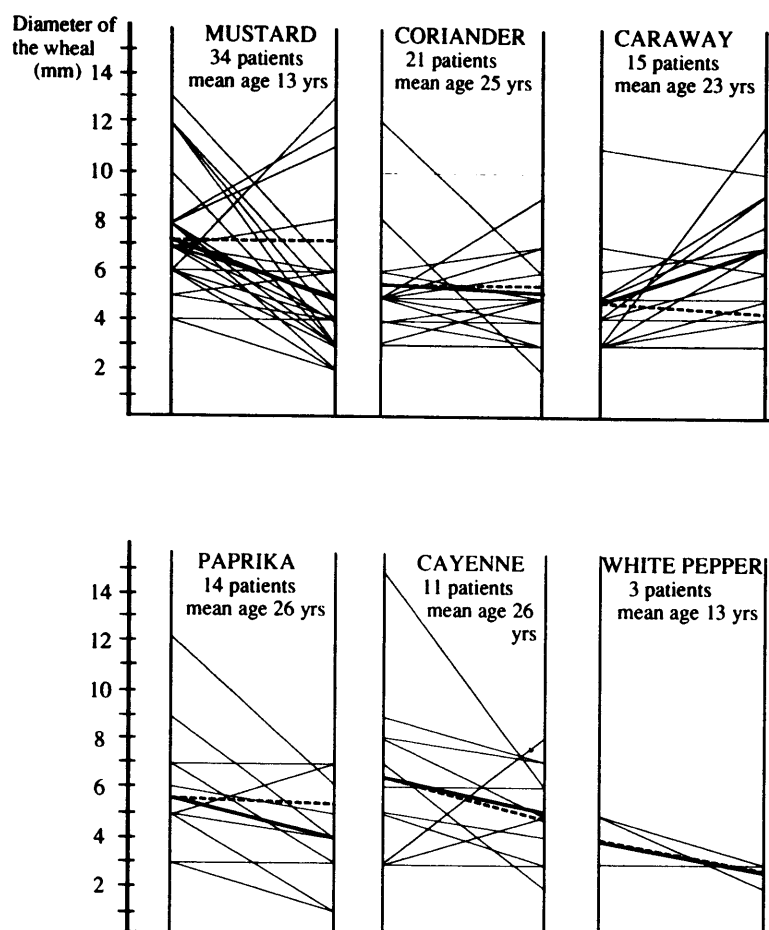


Figure 1. Results of repeated skin prick tests with native spices made at 2 months-2.9 year intervals in 49 patients. Second tests were made in patients in whom the first test was positive with the particular spice. The left and right vertical lines are the first and second test, respectively. (—) Mean values for the spices from Laboratorium Diephuis and (---) mean values for the spices from the kitchen of Oulu University Hospital.

tions were seen with extracts of white pepper (Table 1).

Total and Specific IgE (RAST)

The total serum IgE measured for 48 patients varied from 32 to 4,540 kU/L (mean 745 kU/L) and showed no correlation between test results with native spices or with spice extracts or specific serum IgE. Specific IgE to mustard was measured with the Phadebas RAST method from the sera of 31 skin prick test-positive patients of which 18 were positive. Specific IgE to mustard was then found in the sera of 4/5 Phadebas RAST-negative patients in our immunochemistry laboratory (Helsinki University Central Hospital). Of the 12 caraway-positive cases, three also showed similar differences between the in vitro immunoassay results of Pharmacia and those obtained by one of us (S M-K). Elevated values of specific IgE to mustard were found in 22/31 patients (71%) to coriander in 4/11, to caraway in 7/15, to paprika in 9/12, and to cayenne in 4/8 patients, either at Pharmacia or in our laboratory, mostly with RAST scores 1-2 (≥ 0.35 - < 3.5 PRU/mL; Table 2). Borderline IgE values (≥ 0.30 to < 0.35 PRU/mL) to mustard and caraway were seen in two patients each, to coriander and cayenne in one patient each, but in none to paprika. A specific IgE value of at least 3.5 PRU/mL (RAST score ≥ 3) was noted in three patients, all of whom had positive skin prick tests to the corresponding 1-kD and 8-kD spice extracts but negative to birch and mugwort pollens.

equally often. The 5%-extracts gave positive reactions in 25% to 50% of the cases with positive skin prick

tests to native spices, which was mainly 40% to 75% of those elicited by 10%-extracts. No positive reac-

Table 1. Results of Skin Prick Tests with 10%-, 5%-, and 1%-Spice Extracts with Molecular Weight > 1 kD (1-kD extract) and > 8 kD (8-kD extract) in 46 Patients with Positive Prick Test Reactions from Native Spices

	Tested Patients	1-kD Extract				8-kD Extract			
		No. Positive			Neg. No.	No. Positive			Neg. No.
		10%	5%	1%		10%	5%	1%	
Mustard	31*	19	13	8	12	21	16	12	10
Coriander	20	12	5	3	8	11	6	3	9
Caraway	15	9	4	3	6	10	4	1	5
Paprika	12	8	5	4	4	7	3	2	5
Cayenne	10	5	3	2	5	5	3	2	5
White pepper	2	0	0	0	2	0	0	0	2

* One patient was not tested with 5%- and 1%-extracts.

Table 2. Correlations Between Skin Prick Test Results with Any Spice Extract and 8-kD 5%-Extract, and Specific Serum IgE

Spice	Skin Prick Tests with Any Extract									Skin Prick Tests with 8-kD 5%-Extract								
	Specific IgE									Specific IgE								
	No.	RAST-Scores*					Total		No.	% of Tested	No.	RAST Scores					Total	
		1	2	3	4	5	No.	% of Tested				1	2	3	4	5	No.	% of Tested
Mustard																		
pos	22	5	12	2†	—‡	—	19	86	16	3	11	1	—	—	—	15	94	
neg	9	2	1	—	—	—	3	33	14	4	2	—	—	—	—	6	43	
Coriander																		
pos	9	1	2	1	—	—	4	44	4	1	—	1	—	—	—	2	50	
neg	2	—	—	—	—	—	—	—	7	—	2	—	—	—	—	2	29	
Caraway																		
pos	10	—	3	1	—	—	4	40	4	—	1	1	—	—	—	2	50	
neg	5	1	2	—	—	—	3	60	11	1	4	—	—	—	—	5	45	
Paprika																		
pos	9	3	4	—	—	1	8	89	3	—	2	—	—	—	1	3	100	
neg	3	1	—	—	—	—	1	33	9	4	2	—	—	—	—	6	67	
Cayenne																		
pos	4	1	—	—	—	1	2	50	2	—	—	—	—	—	1	1	50	
neg	4	1	1	—	—	—	2	50	6	2	1	—	—	—	—	3	50	

* RAST scores: 1: 0.35–<0.7 PRU/mL; 2: 0.7–<3.5 PRU/mL; 3: 3.5–<17.5 PRU/mL; 4: 17.5–<50 PRU/mL; and 5: ≥50 PRU/mL.

† One was not tested with 5% and 1% extracts.

‡ None.

Cross-Reactions Between Spices, Fruits, Vegetables, and Pollens

Concomitant reactions to native spices were seen in 19/29 patients in whom all six spices were tested; 14/21 patients with positive reactions to coriander were also positive to caraway, and 9/14 paprika-positive patients were also positive to cayenne. Of the 15 patients with positive tests to mustard, 13 had concomitant positive tests to some other spices, but with no correlation between the spices. Of the 26

patients prick-tested with fruits and vegetables, one-half were positive, most often to celery root. The correlations between the different spices, fruits, and vegetables are shown in Table 3.

All patients with positive reactions to fruits or vegetables were allergic to birch pollen and five also to mugwort pollen. Of the 46 patients with positive skin prick tests to native spices in the latter test, 38 (83%) were positive to birch pollen and eight (17%) also to

mugwort pollen. None of the patients reacted to mugwort pollen without a simultaneous reaction to birch pollen. The numbers of respective birch and mugwort allergies were 371 (11%) and 62 (2%) of all the 3,244 patients tested during the recruitment period of January 1, 1988 to September 30, 1990. Eight patients with positive skin prick tests to native spices and to 8-kD spice extracts were negative to the pollens; three were also tested with fruits and vegetables with negative results.

Table 3. Correlations* Between the Skin Prick Test Results with Spices, Fruits, and Vegetables in 26 Patients Tested with Native Spices, and Fresh Fruits and Vegetables

	Cor†	Car	Pap	Cay	Mus	Whp	Celeriac	Apple	Carrot	Potato
Caraway	0.48									
Paprika	0.13	0.38								
Cayenne	0.01	0.19	0.52							
Mustard	0.02	0.03	0.10	0.33						
Whp	0.12	0.18	0.20	0.24	0.18					
Celeriac	0.27	0.29	0.10	0.00	−0.03	0.25				
Apple	0.40	0.02	−0.02	−0.13	−0.30	−0.15	0.58			
Carrot	0.17	−0.05	0.05	0.27	0.12	0.30	0.67	0.39		
Potato	0.23	−0.03	0.25	0.28	0.18	−0.09	0.31	0.36	0.41	
Swede	−0.09	0.09	0.15	0.18	0.33	−0.07	0.20	0.24	0.28	0.18

* Pearson's r.

† Cor = coriander, Car = caraway, Pap = paprika, Cay = cayenne, Mus = mustard, Whp = white pepper, and Celeriac = celery root.

Clinical Symptoms and Signs from Ingested Spices

Sixteen patients had noticed symptoms from eating spiced food: five from mustard sauce, two from fresh paprika, and nine from strongly spiced ("hot") food or mixed-spice sauces. The symptoms were mild and mostly occurred immediately after the meal. Eight patients reported erythema on the cheeks or around the mouth, one of whom had perioral urticarial lesions. Two patients reported irritation of the eyes or nose; two, itching or burning of the mouth or throat; one, had erosions on the buccal mucosae; two, burning of the throat or chest; and four, exacerbation of atopic dermatitis. In addition, one patient reported exacerbation of hand dermatitis after handling spices when cooking. The clinical symptoms and signs did not correlate with the results of skin prick tests with spice extracts or spice specific IgE results. It was not possible to differentiate between the irritant and allergic types of reaction reported by the patients.

DISCUSSION

In the present study, the reproducibility of skin prick test reactions to native spices was fairly good after 2-month to 2.9-year intervals. The discrepancy seen in the two tests, as well as in the two parallel tests with native spices supplied during the latter test time, could be due to inequalities of the materials under study. The variation in the test material may also partly explain the differences between the in vitro immunoassays done by the Pharmacia laboratories and those done by us. Considerable variations in sulfur compounds have been observed in botanically identical seed specimens of cruciferous plants obtained from different sources.²⁰ In addition, different species of Capsicum fruits of varying sizes and colors are known as paprika and cayenne (also called red pepper, Turkish pepper, chili, and tabasco). Mustard powder usually contains seeds of *Brassica nigra* and *Sinapis alba*, but may sometimes also contain seeds of *B. juncea*. Confusingly, caraway (seeds of *Carum carvi*) and cumin (seeds of *Cuminum cyminum*), both members of

the family Apiaceae, have the same name in Finnish.

Native spices contain irritative substances, eg, isothiocyanates in *B. nigra*, sinalbin in *S. alba*, and capsaicin, the irritant principle of capsicum. Capsaicin also releases substance P, which may cause a non-IgE-mediated mast cell degranulation. These substances may cause skin prick test reactions that are difficult or even impossible to separate from IgE-mediated positives. The point that positive skin tests to native spices were noted in 220/1,120 (20%) atopic and only in 5/380 (1%) nonatopic patients¹ may suggest an atopy-related/IgE-mediated background. The 1-kD cutoff limit of spice extracts used in the present study eliminated any influence of the above mentioned potentially irritative substances characteristic of spice flavors because these substances all have molecular weights <1 kD. The other 8-kD cutoff used is the usual limit in standard skin prick test materials.

The differences between skin prick test results with lyophilized, dialyzed, nonreconstituted extracts and with reconstituted 5%-extracts¹⁶ may have been partly caused by the concentrations of allergen. In the present study, the 5%-extracts gave positive reactions in 25% to 50% of the patients with positive skin prick tests to native spices, which was mainly 40% to 75% of those elicited by 10%-extracts, but few differences were seen between the results from the 1-kD and 8-kD extracts. Similarly, skin prick tests and scratch tests with fresh vegetables are superior to intracutaneous tests with commercial extracts.^{4,21} Native spices may have contained low-molecular weight substances causing nonspecific reactions, which could have been removed by dialysis. It is also possible that some antigen determinants were destroyed during the extraction or dialysis in the present study. The fact that native spices elicited positive scratch test reactions almost exclusively in atopic persons¹ suggest that these reactions are IgE-mediated and that some weak allergens are lost in the dialysis process. The low-molecular-weight irritant substances of native spices might, however, have some additional influence on the size of

the wheals in the skin tests. This enhancement of the reactions might be more pronounced in atopics than in nonatopics.

Specific serum IgE was detected almost equally in patients with positive and negative skin prick test reactions to spice extracts. Most elevated specific IgE values were in the range ≥ 0.35 to < 3.5 PRU/mL (RAST score 1–2); borderline values were seen only very occasionally. Only five specific IgE values of ≥ 3.5 PRU/mL (RAST score ≥ 3) were seen, all in three patients who were skin prick test-positive to both 1-kD and 8-kD extracts of the corresponding spices. Severe reactions from ingested spices are to be expected in individuals with high specific IgE values.^{10,12,13}

Of our patients, one-third reported mild symptoms from ingested spices but no correlations between the patient history and the skin prick test or in vitro assay results were found. The patient histories gave no hints for differentiating irritant from allergic symptoms; therefore, no conclusions could be drawn from the correlations between the skin test or in vitro assay results and true IgE-mediated allergic symptoms. No symptoms appeared in 20 patients with positive scratch tests to native spices, when peroral challenges with spices were given in gelatine capsules.¹

While the present study was being carried out we saw an additional patient, not included in the series, with severe recurrent urticaria and angioedema from mustard. He had a positive skin prick test to native mustard and to 8-kD 5% and 8-kD 1% mustard extracts with respective wheal diameters of 15, 22, and 17 mm. The specific IgE to mustard in his serum was ≥ 50 PRU/mL (RAST score 5). He was not allergic to birch or mugwort pollen and his total IgE was 166 kU/L. In a patient with spice-induced asthma^{15,22} and in patients with severe clinical symptoms from ingested spices,^{12,13} high elevated specific serum IgE values have also been observed.

The spice reactions in the present study were mostly noted in patients

with birch pollen allergy with or without mugwort pollen allergy. In addition, concomitant test reactions to various spices were often noted, and positive reactions to fresh fruits and vegetables were seen in half the patients with skin prick test reactions to native spices. Common antigens among botanically related spices, eg, coriander, cumin, anise, and dill (*Apiaceae*) have been reported^{22,23} while no common antigens were found among nonrelated spices, eg, coriander (*Apiaceae*), ginger (*Zingiberaceae*), and paprika (*Solanaceae*).¹⁵ Of the species used in our study, paprika, cayenne, and potato belong to the *Solanaceae*, coriander, caraway, celeriac (celery root) and carrot to the *Apiaceae*, and mustard and swede to the *Cruciferae* families.

Recently, a 17-kD allergen common to birch pollen, carrot, celery and *Apiaceae* spices was found.²³ The authors suggested that the allergen may be identical with the 15-kD allergen, profilin, a novel plant panallergen in pollens and various vegetable foods.^{24,25} In the present study, positive spice skin prick tests and in vitro immunoassays were also seen in patients who had allergy to neither birch or mugwort pollens, nor fruits or vegetables. Thus spices, which are originally seeds and fruits, may have common plant as well as species-specific allergens, including the novel panallergen. Van Toorenbergen and Dieges¹⁵—who found specific IgE to coriander, paprika, and mace in a patient without allergy to mugwort or birch pollen—suggested that sensitization by mouth or inhalation may influence the pattern of sensitivities. Vegetable foods were found to contain both clinically nonrelevant crossreacting carbohydrate determinants and clinically relevant 18-kD and 20-kD antigenic determinants.^{26,27} Wüthrich et al²¹ suggested that the capacity of celery to cause clinical symptoms is dependent on the concomitant birch or mugwort allergy. It is apparent that spices also contain allergenic determinants with and without clinical relevance.

In conclusion, native spices elicited positive skin prick test reactions in a number of birch or mugwort pollen-allergic people, some of whom also reacted to fruits and vegetables. Positive spice skin prick tests were also seen in patients without pollen allergies, thus strengthening the idea that spices have species-specific antigenic determinants. Dialyzed extracts of spices produced fewer positive skin prick tests than native spices. Positive specific IgE values of at least 3.5 PRU/mL were observed only in patients reacting to 1-kD and 8-kD spice extracts in skin prick tests. Since patients with severe reactions from spices reported in the literature, as well as the one patient of ours, have had high specific IgE values, and since higher specific IgE values in the present study were noted only in cases with positive prick tests to corresponding spice extracts, the 5%-extracts with a cutoff limit of 8 kD might be effective in identifying those patients at risk for developing severe reactions from ingested spices.

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REFERENCES

1. Niinimäki A, Hannuksela M. Immediate skin test reactions to spices. *Allergy* 1981;36:487-93.
2. Wüthrich B, Hofer T. Nahrungsmittelallergie: das "Sellerie-Beifuss-Gewürz-Syndrom". Assoziation mit einer Mangofrucht-Allergie? *Dtsch Med Wochenschr* 1984;109:981-6.
3. Hofer Th, Wüthrich B. Nahrungsmittelallergien. II. Häufigkeit der Organmanifestationen und der allergieauslösenden Nahrungsmittel. *Schweiz Med Wochenschr* 1985;115:1437-42.
4. Wüthrich B, Dietschi R. Das "Sellerie-Karotten-Beifuss-Gewürz-Syndrom": Hauttest- und RAST-Ergebnisse. *Schweiz Med Wochenschr* 1985;115:358-64.
5. Thiel C, Fuchs E, Maasch H-J, et al. Allergy to spices: cross-reactivity to other allergens. In: Ring J, Burg G, eds. *New trends in allergy II*. Berlin Heidelberg: Springer-Verlag, 1986: 154-71.
6. van Toorenbergen AW, Dieges PH. Demonstration of spice-specific IgE in patients with suspected food allergies. *J Allergy Clin Immunol* 1987;79:108-13.
7. Dietschi R, Wüthrich B, Johansson SGO. Zum sogenannten "Sellerie-Karotten-Beifuss-Gewürz-Syndrom." RAST-Resultate mit neuen Gewürzdiscs. *Z Hautkr* 1987;62:524-31.
8. Stäger J, Wüthrich B, Johansson SGO. Spice allergy in celery-sensitive patients. *Allergy* 1991;46:475-8.
9. Panconesi E, Sertoli A, Fabbri P, et al. Anaphylactic shock from mustard after ingestion of pizza. *Contact Dermatitis* 1980;6:294-5.
10. Widström L, Johansson SGO. IgE-mediated anaphylaxis to mustard. *Acta Derm Venereol (Stockh)* 1986;66:70-1.
11. Leanizbarrutia I, Muñoz D, de Corrés LF. Cutaneous allergy to mustard. *Contact Dermatitis* 1987;17:262-3.
12. Monreal P, Botey J, Pena M, et al. Mustard allergy. Two anaphylactic reactions to ingestion of mustard sauce. *Ann Allergy* 1992;69:317-20.
13. Malet A, Valero A, Lluch M, et al. Hypersensitivity to mustard seed. *Allergy* 1993;48:62-3.
14. Bock SA. Anaphylaxis to coriander: a sleuthing story. *J Allergy Clin Immunol* 1993;91:1232-3.
15. van Toorenbergen AW, Dieges PH. Immunoglobulin E antibodies against coriander and other spices. *J Allergy Clin Immunol* 1985;76:477-81.
16. Niinimäki A, Björkstén F, Puukka M, et al. Spice allergy: results of skin prick tests and RAST with spice extracts. *Allergy* 1989;44:60-5.
17. Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Methods for skin testing. In: Dreborg S, ed. *Skin tests used in type I allergy testing*. *Allergy* 1989;44(Suppl. 10):22-30.
18. Dreborg S, Foucard T. Allergy to apple, carrot and potato in children with birch pollen allergy. *Allergy* 1983;38:167-72.
19. Ceska M, Lundkvist U. A new and simple radioimmunoassay method for the determination of IgE. *Immunochemistry* 1972;9:1021-30.

20. Mitchell JC, Rook A. Botanical dermatology. Plants and plant products injurious to the skin. Vancouver: Greengrass, 1979:227-9.
21. Wüthrich B, Stäger J, Johansson SGO. Celery allergy associated with birch and mugwort pollinosis. *Allergy* 1990; 45:566-71.
22. van Toorenenbergen AW, Huijskes-Heins MIE, Leijnse B, et al. Immuno-blot analysis of IgE-binding antigens in spices. *Int Arch Allergy Appl Immunol* 1988;86:117-20.
23. Helbling A, Lopez M, Schwartz HJ, et al. Reactivity of carrot-specific IgE antibodies with celery, apiaceous spices and birch pollen. *Ann Allergy* 1993; 70:495-9.
24. Valenta R, Duchene M, Ebner C, et al. Profilins constitute a novel family of functional plant pan-allergens. *J Exp Med* 1992;175:377-85.
25. Vallier P, Dechamp C, Valenta R, et al. Purification and characterization of an allergen from celery immunochemically related to an allergen present in several other plant species. Identification as a profilin. *Clin Exp Allergy* 1992;22:774-82.
26. Aalberse RC, Koshte V, Clemens JGJ. Immunoglobulin E antibodies that crossreact with vegetable foods, pollen, and Hymenoptera venom. *J Allergy Clin Immunol* 1981;68:356-64.
27. Calkhoven PG, Aalbers M, Koshte VL, et al. Cross-reactivity among birch pollen, vegetables and fruits as detected by IgE antibodies is due to at least three distinct cross-reactive structures. *Allergy* 1987;42:382-90.

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MULTIPLE ACTUATIONS OF METERED DOSE INHALER INTO SPACER REDUCE DOSE INHALED BY PATIENT

The authors determined the amount of beclomethasone dipropionate contained in particles of various sizes available for inhalation from a 750 mL (volumetric) spacer by impinger measurement and high performance liquid chromatography. They evaluated delivery from metered dose inhalers that released 50 µg, 100 µg, and 250 µg per actuation.

The amount of beclomethasone dipropionate in particles <5 µm in diameter was similar whether delivered via spacer or directly from the metered dose inhaler while the total amount of drug available for inhalation decreased by 20 µg from 50 µg, by 48 µg from 100 µg, and by 161 µg from 250 µg when delivered via spacer. Increasing the number of actuations delivered to the spacer before inhalation to 3, 4, 5, and 10 actuations caused progressive decreases in total drug available for inhalation as well as progressive decreases in drug in particles <5 µm and <3 µm in diameter. Delays of 1, 5, 10, 20, 30, 45, and 60 seconds between actuation into the spacer and inhalation also were associated with progressive decreases in amounts of beclomethasone dipropionate available for inhalation.

These data indicate that when beclomethasone dipropionate is delivered from a metered dose inhaler via spacer it should be inhaled immediately after actuation of the inhaler and multiple actuations into the spacer before inhalation should be avoided.

—RMS

O'Callaghan C, Cant M, Robertson C. Delivery of beclomethasone dipropionate from a spacer device: what dose is available for inhalation? *Thorax* 1994;49: 961-4.