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CLINICAL REPORT

Orange-Induced Skin Lesions in Patients with Atopic Eczema: Evidence for a Non-IgE-Mediated Mechanism

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Oranges are suspected of inducing adverse skin reactions in patients with atopic eczema. We studied 21 adult patients with atopic eczema and a history of adverse reactions to oranges and 10 patients without. A dietary history, skin tests, serum IgE and oral provocation tests with oranges were obtained. Severity of eczema was monitored by SCORAD, and serum tryptase, eosinophil cationic protein and urinary methylhistamine were measured. No allergic reactions were found to orange in skin prick or patch tests. However, 23 patients (74%) had specific serum IgE to orange. Oral provocation testing resulted in pruritic eczematous or maculopapular skin lesions predominantly at the predilection sites in 16 patients (52%). The SCORAD increased significantly in patients positive to the oral provocation test ($p < 0.05$). Specific IgE to orange did not correlate with the clinical outcome of the oral provocation test. No significant changes were found in serum mast cell tryptase, eosinophil cationic protein or in urinary methylhistamine excretion. The negative results in the skin tests and a lack of correlation between specific IgE and oral provocation tests indicate that non-IgE-mediated mechanisms are involved in cutaneous adverse reactions to oranges in patients with atopic eczema. ***Key words: adverse reaction; atopic eczema; IgE; orange; pseudo-allergic reaction.***

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Atopic eczema (AE) is a chronic or relapsing intensely pruritic eczematous skin condition (1), but the role of food hypersensitivity is still a matter of controversy (2–4). The frequency of food hypersensitivity is correlated with severity of the disease, and, using a double-blind placebo-controlled food challenge, has been found to affect 63% of children with severe AE (5). Citrus fruit and food preservatives are often accused of deteriorating the course of AE in predisposed patients, and oranges are among the most commonly mentioned foods. However, although this issue is clinically important, reliable studies are lacking (6, 7). To elucidate the influence of oranges in severe adult AE, and to investigate the underlying pathomechanisms, we performed a prospective allergologic study using the patient's history, skin tests, *in vitro* tests and oral provocation test (OPT) in a group of patients with a history of adverse reactions to oranges and in a comparable group without such reactions.

MATERIAL AND METHODS

Patients

Thirty-one patients, 12 males and 19 females with long-standing and severe AE aged 18 to 42 years (mean age 29 ± 5 years), were hospitalized in Davos/Switzerland and enrolled in the study. The patients were in a stable phase of partial remission (32 points $\pm$ 13 in the SCORAD (Severity Scoring of Atopic Dermatitis) assessment) (8). They did not receive systemic medication nor topical steroids, so allergy testing was possible. The study was in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1996, and informed consent was obtained from the patients prior to enrolment.

Four of the 31 patients (13%) suffered from AE as a single manifestation of atopy, 3 (10%) had bronchial asthma, 7 (23%) had allergic rhinoconjunctivitis and 17 (55%) had both bronchial asthma and allergic rhinoconjunctivitis in addition to AE.

History

A detailed history was taken using a standardized questionnaire with special emphasis on provocation factors for eczematous skin lesions including adverse reactions to oranges and citrus fruit.

Skin tests

Skin prick tests (SPT), rub tests and patch tests were performed according to international standards (9). An SPT was done on the volar forearm with commercially available orange extract and standard allergen extracts (Scherax, Hamburg, Germany) and with ascorbic acid and citric acid (1 g/100 ml in physiologic saline). Prick tests with different parts of fresh oranges (seeds, pulp and peel) were done by pricking with a prick test needle first into a fresh slice of fruit

Table I. *Baseline characteristics (mean ± SD) of atopic eczema patients with and without history of adverse reactions to oranges*

History of reaction to oranges	No. of patients	Age (years)	Sex	Total serum IgE (kU/l)	Specific serum IgE to oranges (kU/l)	SCORAD
Positive group	21	28.4 ± 5	16F/5M	1025 ± 2882	1.3 ± 5	31.6 ± 13
Negative group	10	30.6 ± 4	3F/7M	1938 ± 1717	2.3 ± 6	32.5 ± 14
Total	31	29.1 ± 5	19F/12M	1259 ± 2566	1.6 ± 5	31.9 ± 13

SCORAD = severity scoring system of atopic dermatitis (maximum points 103).

and immediately afterwards into the skin. Rub tests were performed by rubbing parts of fresh oranges 20 times on the volar forearm. Controls were with rubbing sterile gauze. Fresh oranges, as well as orange oil, dipenten, cinnamonic aldehyde, citronellal, eugenol and perubalsam (Hermal, Reinbek, Germany) were used for patch tests in each subject. SPT and rub tests were read after 20 min, patch tests after 20 min, 48 h and 72 h.

In vitro allergy diagnosis

Serum levels of total and specific IgE to orange were measured using the CAP RAST FEIA system (Pharmacia, Uppsala, Sweden). Specific IgE to the cross-reactive carbohydrate determinant MXF^3-GP isolated from bromelain was determined as described previously (10).

For biochemical monitoring of inflammation, serum mast cell tryptase was determined by UNICAP FEIA and eosinophil cationic protein (ECP) by CAP ECP FEIA (Pharmacia, Uppsala, Sweden) before, 2 h and 24 h after OPT. Methylhistamine was determined in urine collected 24 h before and 24 h after OPT (pH-adjusted with 10 ml of 6N hydrochloride) and determined by radioimmunoassay (Pharmacia, Uppsala, Sweden) (11). Serum and urine samples were prepared according to guidelines and stored at −20°C until analysis (12).

Oral provocation test (OPT)

Strict avoidance of citrus fruits and histamine-rich foods was introduced 2 days prior to the study. OPT was performed 2 h after a light breakfast. Orange juice was prepared immediately before the OPT using juice, including pulp from freshly squeezed oranges. After oropharyngeal application of 25 ml and 1 min contact, a total amount of 200 ml was swallowed.

The symptoms were monitored before OPT and over the ensuing 48 h by the same investigator. Subjective symptoms, such as pruritus, oropharyngeal itching and swelling, were noted by the patients and objective signs, such as erythematous macular rash, flare of the eczema, or rhinitis, were recorded and the severity of the eczema was evaluated by SCORAD at 6, 24 and 48 h (8). Development of new cutaneous lesions of more than 5% body surface or an increase of the SCORAD of more than 10% at any time within the 48 h observation period following the OPT was considered a positive reaction.

Statistical analysis

Statistical analysis was performed on pooled demographic and outcome data. If not mentioned otherwise mean values ± standard deviations are given. For total and specific serum IgE geometric means were calculated. A two-sided *t*-test for unequal variances was used for comparisons between study groups and within a group. Concordance between the total serum IgE and specific IgE against orange was analysed using Spearman's correlation coefficient. Positive predictive value was calculated by dividing the number of positive OPTs with a positive history by the total number of positive histories of adverse reactions to oranges. The negative predictive value was determined by dividing the number of negative OPTs with negative history by the total number of patients with negative histories. For comparison of different variables a *p*-value of less than 0.05 was considered statistically significant.

RESULTS

History

Of the 31 patients with AE who participated in the study, 21 (68%) had a history of adverse reactions following ingestion of oranges and 14 of these patients (67%) also had reacted to other citrus fruits. The reported symptoms consisted of generalized pruritus (100%), erythematous patches or wheals (52%), deterioration of eczema (38%) and nausea (5%). The symptoms were related to the amount of fruits consumed in 15 patients (71%) and occurred within 1 h after consumption in 14 patients (67%) and within the next 24 h in 7 patients (33%). Oropharyngeal symptoms had been present in 6 patients (29%). Demographic data of patients, total and specific IgE levels and the SCORAD in patients with and without a history of adverse reactions to oranges are presented in Table I.

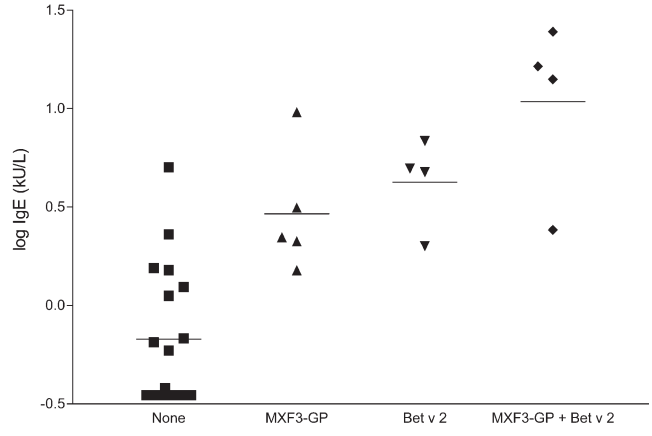

Fig. 1. Specific IgE levels to oranges (individual values and mean value) were significantly higher in patients with specific antibodies to MXF3-GP ($p = 0.007$), with antibodies to birch pollen profillin Bet v 2 ($p = 0.006$), or with antibodies to both determinants ($p = 0.003$) compared to 18 patients without such antibodies.

Skin tests

In the rub and patch tests with oranges no positive reaction could be elicited in any patient. Thirty patients (97%) had at least one SPT reaction (median = 8) out of 16 standard allergens. In the prick-to-prick test, wheals with a diameter of 2–3 mm were observed to orange seeds, orange pulp, orange peel, or to the commercially available orange extract in 15 patients (58%). However, the reflex erythema was lacking in all patients. Similar reactions were also elicited in healthy controls without adverse reactions to oranges (data not shown), and the reactions were regarded as irritative. The pH of oranges was constantly between 3 and 4.

In vitro tests

The mean total IgE was 1259 kU/l and mean specific IgE to oranges was 1.6 kU/l (Table I). Total and specific IgE were higher in patients without a history of adverse reactions to oranges (Table I, n.s.). There were significantly higher specific IgE levels to oranges in patients with high total IgE ($r = 0.53$, $p < 0.002$) (data not shown). All patients with allergic rhinoconjunctivitis and antibodies to pollen had specific IgE values to oranges. To investigate a possible cross-reactivity of specific IgE to oranges with antibodies found in pollen-induced food allergy, the presence of antibodies to Bet v 2 and the carbohydrate determinant MXF3-GP were studied. Specific IgE levels to oranges were significantly higher in patients with antibodies to MXF3-GP, to birch pollen profilin Bet v 2 and/or compared with 18 patients without demonstrable antibodies to these determinants (Fig. 1).

Oral provocation test

Sixteen of 31 patients (52%) reacted to 200 ml freshly squeezed orange juice with objective and subjective symptoms (Fig. 2, Table II); another 6 patients (19%) developed subjective symptoms (pruritus, oropharyngeal symptoms) only. All objective skin reactions were pruritic (Table II). Skin areas most often affected by the reactions were flexures of the elbows, forearms, face and neck. In 6 patients (19%), skin symptoms were combined with oropharyngeal itching and swelling of the lips, oral mucosa or pharynx. Thirteen of 16 objective reactions (81%) occurred within 1 h after the OPT and 3 (19%) within 12 h after OPT. Duration of the symptoms was ≤ 2 h in 3 patients, ≤ 24 h in 9 patients and > 24 h in 4 patients. In the patients reacting to oranges, the severity of the eczema increased significantly after OPT as measured by SCORAD from 29.5 ± 16 before OPT to 32.3 ± 16 after 6 h ($p < 0.01$), and to 32.8 ± 13.9 after 24 h ($p < 0.05$) followed by a decrease to 31.9 ± 15.7 at 48 h.

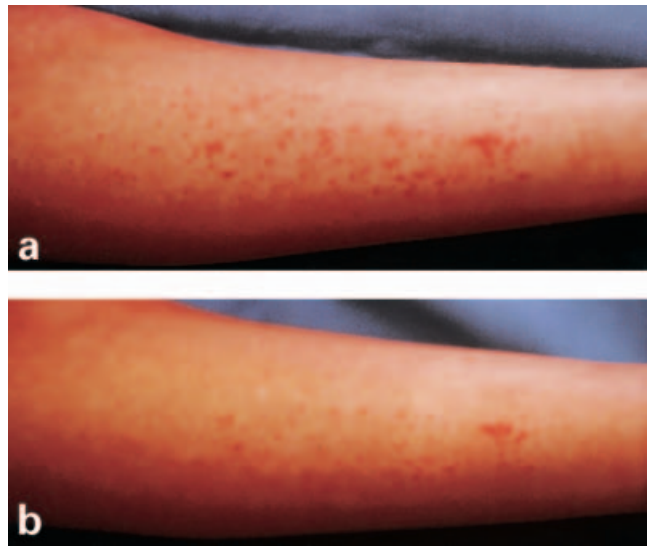

Fig. 2. Newly developed eczematous skin lesion on the left forearm (a) 6 h after oral provocation test and (b) improvement seen after 48 h.

Table II. *Objective clinical symptoms in 16 patients with atopic eczema after oral provocation test with orange juice*

Age/sex	History: reaction to oranges	Clinical symptoms	Onset (min)	Duration (h)
32/M	+	P, E	5	0.5
33/F	+	P, E, OPS	50	10
27/M	−	P, ER, E	50	24
27/M	−	P, ER, E	30	24
30/M	+	P, E, OPS	50	6
38/M	−	P, ER, E, OPS	30	24
19/F	+	P, UR,MPR, E	30	7
32/F	+	P, ER, OPS	20	6
33/F	+	P, E	15	0.7
21/M	+	1. P, ER, OPS	15	0.5
		2. Facial erythema[a]	1200[a]	48[a]
24/F	+	P, MPR	720	48
23/F	+	P, E	45	24
35/F	+	P, ER, E	20	6
23/F	+	P, ER, E	40	2
27/F	+	P, MPR	300	24
28/M	+	P, ER, OPS	720	72

P = generalized pruritus; ER = erythematous rash; MPR = maculopapular rash; UR = urticarial rash; E = deterioration of pre-existing eczema or appearance of new eczema; OPS = oropharyngeal symptoms; [a]biphasic reaction.

Inflammatory mediators

Mean serum concentration of ECP in patients with positive OPT was increased 2 h after OPT from 18.6 ± 12.1 µg/l to 21.2 ± 18.0 µg/l and decreased again to 18.0 ± 13.7 µg/l after 24 h. This was not statistically significant. However, an increase 2 h after OPT was also observed in patients with negative OPT and differences were not statistically significant. Serum mast cell tryptase prior to OPT was significantly higher ($p < 0.05$)

in patients with positive OPT than in patients with negative OPT (6.8 ± 5.2 μg/l versus 3.8 ± 1.7 μg/l). No significant change was observed in serum tryptase within 24 h after OPT in either group. Urinary methyl-histamine was 162 ± 127 μg/l per 24 h in patients with positive OPT and 147 ± 115 μg/l in patients with negative OPT (n.s.). No increase was observed following the OPT.

Comparison of results with patient history and orange-specific IgE

Thirteen of 21 patients with a positive history of adverse reactions to oranges had specific IgE to oranges compared with 7 of 10 patients with negative history (n.s.). The positive predictive value of patient history was 62% while the negative predictive value was 70%. There was no correlation between orange-specific IgE to the results of OPT, positive and negative predictive values being 53% and 50%. Ten of 16 patients with positive OPT and 9 of 15 patients with negative OPT had a specific IgE class of 2 or higher. Mean specific IgE to oranges in patients with positive OPT (1.4 kU/l) did not differ significantly from patients with negative OPT (1.7 kU/l).

DISCUSSION

In this prospective study of 21 patients with AE and a history of adverse reactions to oranges, compared with 10 patients with no history of orange hypersensitivity, adverse reactions and exacerbations of eczema were induced in 52% of patients by OPT with freshly squeezed orange juice (Table II, Fig. 2). Patient history was unreliable, because positive and negative predictive values were 62% and 70%, respectively. There were no specific skin test reactions to oranges in patients with AE. Levels of specific IgE to oranges were higher in patients with no history of adverse reactions to oranges (Table I) and did not correlate with the results of the OPT. The presence of specific IgE to oranges was correlated to the presence of specific IgE to birch pollen, profillin Bet v2 and to the carbohydrate pollen determinant MXF3-GP (Fig. 1) and also with total serum IgE.

Citrus fruits are considered to trigger a worsening of AE (14–18). In the literature, the incidence of reactions to oranges and citrus fruits has been reported to occur in between 1.4% and 48.5% in paediatric or adult patients with atopic conditions, reflecting big differences in patient populations and study designs (7, 13). However, in these studies only data from the patient's history were presented, or the diagnostic methods were not described in detail (13–18). The higher incidence of adverse reactions to oranges of 52% in this study may in part reflect the fact that we selected patients with a positive history of adverse reactions to oranges and compared them with a smaller group of patients without this history. In addition, open OPTs are generally considered to be less reliable than double-blind placebo-controlled food challenges (19), but it enabled us to give a total volume of 200 ml freshly squeezed orange juice, including pulp, without the problem of reliable blinding. Furthermore, all patients in the rehabilitation centre had long-standing and severe AE, which may also lead to a higher incidence of adverse reactions to foods and food additives (20).

In the SPT with native oranges and commercially available extracts, some patients showed small wheals after 10 to 15 min. However, these phenomena were all considered irritative as the diameter of the wheals was lower than 3 mm in all cases, the erythema flare was absent, and similar reactions were also observed in non-atopic controls. Although positive skin test reactions to oranges have been described in the literature (17), they have also been considered as irritative or carrying no clinical significance by others (16). In the patch test, no positive reactions were found to native oranges, as described for positive atopy patch tests to cow's milk, egg and cereals (21).

Orange-specific IgE was detected in the majority of subjects, but levels did not correlate to the results of OPT nor to the history, but to total serum IgE ($p < 0.002$) and sensitizations to the commonly cross-reacting pollen allergens bet v2 and MXF3-GP (Table II). Cross-reactivity and unspecific binding may be possible reasons for this phenomenon also observed by others (18).

Serum mast cell tryptase, ECP and MPO, as well as urinary methyl-histamine, may be markers for food allergy (20). We found no increase of these parameters in patients with positive OPT only. An increase in ECP was also observed in patients with negative OPT. Our results are in accordance with others, who have demonstrated no correlation of atopic eczema severity to serum ECP, nor to tryptase levels (22). However, other investigators have found a correlation between ECP and severity of eczema, and after oral challenges with food allergens (23, 24). Oranges have also been considered to cause unspecific mast cell degranulation *in vitro* (25, 26), and in our study we observed unspecific reactions in the skin prick test. However, increased circulating levels of mast cell mediators have never been demonstrated *in vivo* after ingestion of oranges as confirmed in this study.

Pseudo-allergic reactions elicited by salicylic acid, citric acid or ascorbic acid naturally occurring in oranges have been considered (6, 27). Food intolerance due to the enzymatic or pharmacological action of biogenic amines in oranges, such as tyramine, putrescine and synephrine, might be other possible mechanisms, and oropharyngeal symptoms observed after contact to oranges have been considered to be irritative and to be caused by the acidic pH of oranges or by etheric oils (28, 29).

In conclusion, in patients with severe AE, objective

adverse reactions to oranges could be demonstrated by a standardized open OPT. These reactions are not dependent on IgE. Currently, OPT is the only test for the diagnosis of adverse reactions to oranges. In future, attempts to blind orange juice should be undertaken to allow double-blind placebo-controlled food challenge. Further studies are necessary to investigate the pathomechanism of adverse reactions to oranges in patients with atopic eczema.

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