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Food-induced contact urticaria syndrome (CUS) in atopic dermatitis: reproducibility of repeated and duplicate testing with a skin provocation test, the skin application food test (SAFT)

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IgE-mediated contact urticaria syndrome (CUS) is one of the manifestations of allergy in childhood atopic dermatitis (AD). Allergens such as foods and animal products penetrate the skin easily. They can then cause urticarial reactions in sensitized individuals. A provocation test system for foods, called the skin application food test (SAFT), has been developed. Over more than 5 years, a group of 175 patients with AD was built-up and investigated in a prospective follow-up study with SAFT. SAFT was more frequently positive in AD children aged 0–2 years than in older children. In several children of this population (Group 1), we repeated SAFT within a period of 1 year. In another unrelated group of children (Group 2-1), we compared the results of 'original' SAFT and SAFT using square chambers (Van der Bend) or Silver patches. In the 3rd group (Group 2-2) we compared 'original' SAFT with SAFT using big Finn Chambers. The agreement between the tests was high: in Group 1, we observed 88 to 93% concordant scores, and in Group 2, the scores were 96% to 100%. Statistically, the κ coefficient ranged from 0.71–0.87 in Group 1, and from 0.83–1.00 in Group 2. SAFT is therefore highly reproducible. Agreement was at least $\geqslant$88% between the scores (the lowest κ value observed was at least 0.71).

Key words: foods; contact urticaria syndrome; atopic dermatitis; children; skin application food test; cow's milk; egg; peanut; van der Bend square chambers; big Finn Chambers; Silver patches.
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The term contact urticaria syndrome (CUS) was introduced in 1975 (1, 2). Contact urticaria is a weal-and-flare response to agents rapidly absorbed via intact skin. The incidence of contact urticaria in patients with atopic dermatitis (AD) is unknown (3, 4). The combination of AD and CUS has been unrecognized for many years. IgE-mediated CUS due to food (and animal dander) allergens is a major cause of allergy in childhood AD (5). The role of IgE in CUS and childhood AD is important.

Food allergens such as cow's milk, egg and peanut, among others, penetrate the skin easily (4, 6, 7). In sensitized individuals, this results in an urticarial reaction. Such reactions can evolve into generalized anaphylactic reactions, even with shock (6, 7). A provocation test system, called the skin application food test (SAFT), has been developed. For more than 7 years, we have used SAFT in children up to 4 years old with AD.

This article presents the results of patch testing for food-induced immediate contact allergy: duplicate and reproducible testing of SAFT using 'original' patches and SAFTs using other chambers. We evaluated square chambers (van der Bend) or silver patches and big Finn Chambers.

Materials and Methods

Patients

In a longitudinal follow-up study in 175 patients with AD (5), SAFTs were repeated after 1 year.

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The purpose was to determine whether CUS could still be provoked. Group 1 was subdivided according to allergen, cow's milk (Group 1-1), egg (Group 1-2), peanut (Group 1-3). In 2 other groups (2-1 and 2-2), we compared the results of 'original' SAFT with the results of SAFT using other systems. The different systems were square chambers (van der Bend), Silver patches (Group 2-1) and big Finn Chambers (Group 2-2).

Group 1. In children with CUS induced by cow's milk (Group 1-1, $n=52$), egg (Group 1-2, $n=52$), or peanut (Group 1-3, $n=51$), SAFT was repeated after 1 year. Only the results of the 1st and the 2nd tests were included in this study. When CUS was no longer present, we performed oral challenges as described (5). Patients who lost their allergy (as proven by oral challenge) were excluded from this study. However, doubtful cases were included.

Group 2. We compared different methods of testing: the 'original' SAFT method and other different patch systems. Group 2-1 consisted of 33 children. Van der Bend chambers and Silver patches were evaluated in 20 and 13 children, respectively. In Group 2-2, 'original' SAFT was compared with the big Finn Chamber SAFT method in 35 children. Cow's milk and egg were applied as allergens in both the subgroups 2-1 and 2-2. Cow's milk and egg tests (SAFT) were mutually independent within a patient.

SAFT

The original test was performed as described before (8). 4 cm^2 gauze containing food (0.8 ml solution or a solid slice of allergen) or control fluid (0.8 ml of 0.9% sodium chloride) was used. These patches were applied to a skin area cleansed of fat with 96% alcohol. The gauzes containing foods (0.8 ml or a slice) were fixed to the skin with Finn Chamber Scanlon® plasters (Norgesplaster A/S, Oslo, Norway). Patch tests were examined at intervals of 10 min. The maximum time of application was 30 min. Scores of 0 and 1+ (only redness) were regarded as negative. Reactions of 2+ (redness & oedema) and 3+ (redness & oedema covering 4 cm^2 or more) were regarded as positive (Figs. 1, 2).

Besides the 'original' SAFT described above, we also performed SAFTs with other patch test systems. These methods differ from the original test (4 cm^2) in the area covered, ranging from 0.25 cm^2

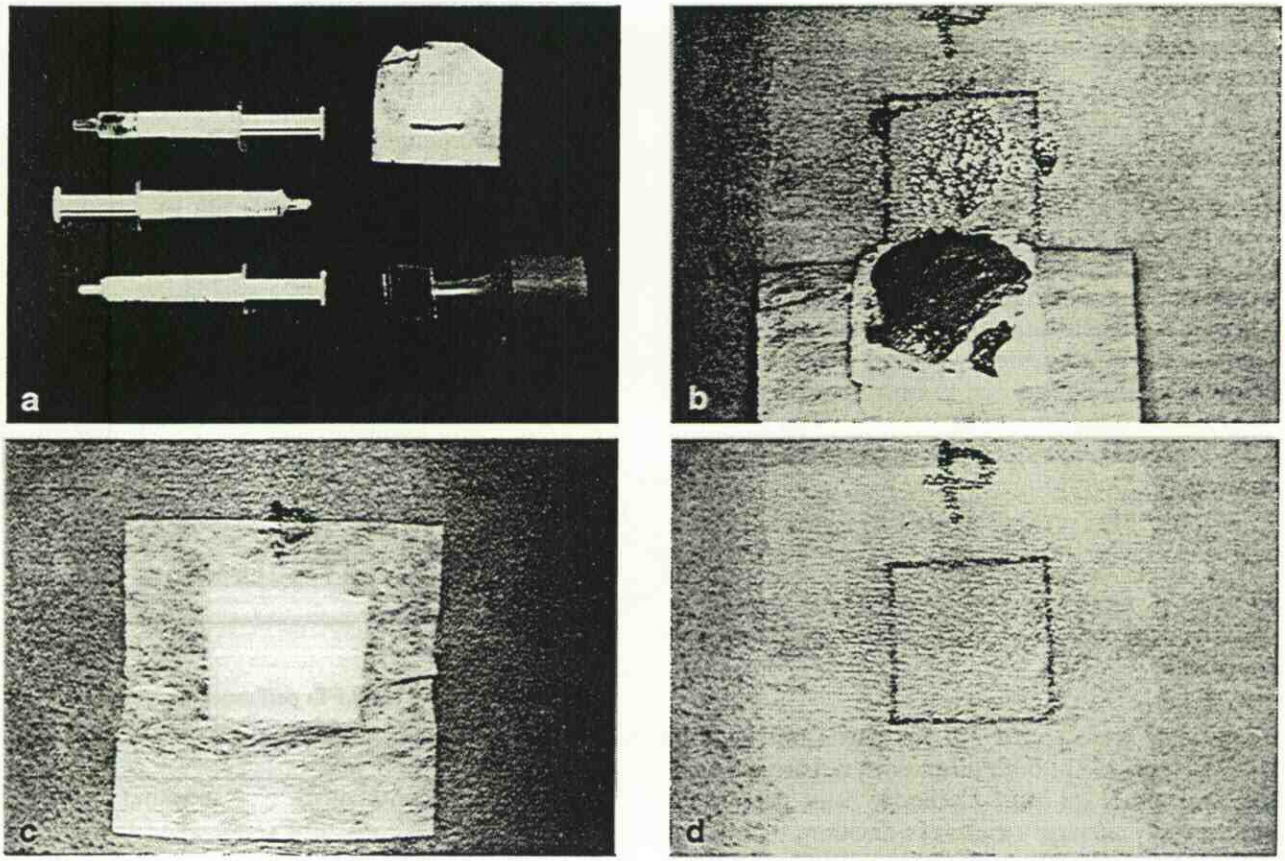

Fig. 1. Presentation of SAFT: (a) equipment; (c) fixation to the skin; (b) reading; (d) positive reaction scored as 3+.

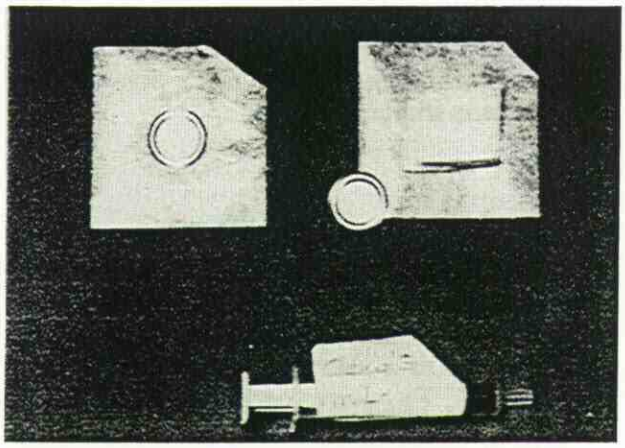

Fig. 2. 'Original' SAFT and SAFT using big Finn Chambers.

(Van der Bend square chambers, Silver patches) to 1 cm^2 (big Finn Chambers).

Oral food challenge tests

In the case of discrepancies between the clinical history and SAFT results, patients were challenged orally with the involved allergens. The open oral provocations were performed in the day-care ward or in the inpatient clinical ward as described before (5). (Under the age of 3 years we perform open challenges. When the children are older, the oral challenges are performed double-blind placebo controlled.)

Statistical analysis

The κ coefficient was used to measure the agreement between the test results of the various method (9). $\kappa = 0$ under statistical independence, and $\kappa = 1$ with complete agreement.

κ values higher than 0.75 are considered to represent excellent agreement beyond chance. Values below 0.40 are considered to represent poor agreement beyond chance, and values between 0.40 and 0.75 represent fair to good agreement (beyond chance) (9).

Results

Results of tests repeated after 1-year period, in children with contact urticaria from egg, peanut and cow's milk

Group 1-1

52 patients were tested 2× for cow's milk within a 1-year period. In 6 children with negative SAFT the 2nd time, an oral challenge was performed without any adverse results. In another, 3 children with negative SAFT the 2nd time, it was uncertain whether they were still allergic or not. Oral challenge was omitted in 2 patients (because of the mother's fear about the possible outcome and because of oral corticosteroid therapy for asthma, respectively).

Thus, repeated SAFT testing was assesed in 46 cases, including the 3 cases in which oral challenge was not performed (Table 1). The other 6 cases were excluded from the comparison, because the tests were not duplicates.

The agreement between the results was 93% (43/46). The observed number of patients with concordant test results was 43: by chance, this number equalled $(23+20)-2(23\times 20/46-3\times 0/46)=43-20=23$. The estimated κ is $43-23/46-23=20/23=0.87$. The 95% confidence interval is 0.64 to 0.97.

Group 1-2

52 patients were tested 2× for egg in a period of 1 year. In 3 children with negative SAFT the 2nd time, an oral challenge was successfully performed without any adverse reaction. 1 child developed egg allergy, but could eat egg before without any problems. These 4 cases were excluded from the comparison, because the test results were not considered duplicates.

Repeated SAFTs were assessed in 48 children, including 2 children in whom an oral challenge was refused. A 3rd child was included, in whom 1 year earlier, egg allergy could not be clearly recognized (Table 2).

The agreement between SAFT results with egg was 94% (45/48). The observed number of patients with agreed test results was 45: by chance this number is expected to be $(37+8)-2(37\times 8/48-2\times 1/48)=32.8$. The estimated κ is 45-32.8//48−32.8 = 12.2/15.2 = 0.80. The 95% confidence interval is 0.40 to 0.93.

Table 1. Comparison of SAFT performed with cow's milk, before and after a period of 1 year

Cow's milk	2nd time	SAFT	
1st time	+ (positive)	− (negative)	
SAFT +	20	3	
−	0	23	
			46

Table 2. Comparison of SAFTs performed with egg before and after a period of 1 year

Egg	2nd time:	SAFT	
1st time:	+ (positive)	− (negative)	
SAFT +	37	2	
−	1	8	
			48

Table 3. Comparison of SAFTs performed with peanut, before and after a period of 1 year

Peanut	2nd time: SAFT	
1st time:	+ (positive)	− (negative)
SAFT +	20	2*
−	4	24
		50

* 1 case positive when repeated on eczematous skin.

Table 4. Comparison of SAFT performed in the 'original' way and with van der Bend Chambers or Silver patches

	Small patch SAFT		
	+ (positive)	− (negative)	counted
original SAFT			
+	20	5	25
−	0	39	39
counted	20	44	64

Table 5. Comparison of 'original' SAFT with Finn Chamber SAFT with cow's milk and egg.

	Big Finn Chamber SAFT		
	+ (positive)	− (negative)	counted
original SAFT			
+	22	0	22
−	0	43	43
counted	22	43	65

Group 1-3

This group with peanut allergy consisted of 51 patients. In 1 case, peanut allergy had certainly developed later. This case was excluded from the comparison, because the test was not a duplicate.

Therefore, repeated SAFT was evaluated in 50 children. In 4 cases, the 2nd SAFT performed was positive while the 1st test was negative. In 2 cases, possible though not convincing explanations included oral prednisone therapy and later sensitization.

In one of the 2 cases with positive 1st SAFT and negative 2nd test, the mother of the child concerned refused oral challenge. In the other, the test was positive when repeated on eczematous skin.

Agreement between the results was 88% (44/50). The observed number of patients with concordant test results was 44: by chance this number is expected to be 25. The estimated κ is $(44-25.1)/(50-25.1)=0.76$. The 95% confidence interval is 0.51 to 0.91 (Table 3).

'Original' SAFT versus SAFT using van der Bend Chambers, Silver patches or big Finn Chambers for egg and cow's milk

Group 2-1

In 33 patients, 64 tests were performed with 'original' SAFT, 'micro' SAFT with van der Bend chambers in 20 patients, and with Silver patches in 13 patients. Cow's milk and egg tests were mutually independent within a patient. Cow's milk and egg were tested in these patients (except 1 patient, who was tested with egg alone).

The calculated agreement of the results was 92% (59/64). The observed number of patients with concordant test results was 59: by chance this number equalled 34.6. The estimated κ was $(59-34.6)/(64-34.6)=24.4/29.4=0.83$. The 95% confidence interval is 0.62 to 0.94 (Table 4).

Group 2-2

In 35 patients, 65 tests were performed with 'original' SAFT and SAFT using big Finn Chambers. The tested allergens were cow's milk and egg (2 patients not tested with cow's milk and 3 patients not tested with egg). Cow's milk and egg tests were mutually independent within a patient (Table 5).

In this series of tests, complete agreement (100%) was observed. The number of concordant results expected by chance is 35.9. κ is estimated as 1.00, with a 95% confidence interval of 0.88 to 1.00.

Discussion

SAFT is a suitable test in small children with atopic dermatitis (AD). For infants and toddlers, it is sensitive and child-friendly. The symptoms of food allergy FA are variable from one target organ to another (10). Urticarial flare-ups are common in small children with AD. When the skin is involved, contact urticaria (CUS) is a common and major symptom in small children though not exclusive to them. Although CUS is easily recognized, mothers are often confused and are unable to indicate precisely the correct allergens that are involved. Therefore, SAFT is more than a routine skin test, because it imitates the events that occur in daily life. However, the sensitivity of SAFT diminishes in older children aged 4 years or more (unpublished observations).

The results presented here illustrate that SAFT is highly reproducible. The results are at least comparable with those of prick testing (11). The agreement of SAFT results was at least $\geqslant 88\%$ in the scores. Our results of SAFT are in reality even better than presented. Refusal of the parents to conduct an oral challenge, or oral prednisone ther-

apy and other factors, led to lower conclusive results in various series in sub-geroups 1-1, 1-2 and 1-3. For example, 2nd SAFT performed for peanut was positive in 4 cases, while the 1st test was negative. In 2 cases, we thought we could explain this, though not with certainty. The other 2 could have been sensitized later, as in one of the others. Doubtful cases, such as those illustrated, were included and lowered the values of agreement and κ.

Prick testing was significantly less reproducible in cases with severe eczema compared with cases with mild eczema. A lack of reactivity to food allergens was observed (11). This could have been due to lack of quality of the extracts and non-IgE-dependent mechanisms of mast cell release. Such adverse factors do not play a role in the interpretation of SAFT. In SAFT, no extracts are used, but foods are applied in the same form in which they are consumed. A major disadvantage of SAFT is its limited use in older children aged 4 years and more. Reliable application of SAFT is assured in children aged up to 3.

The results of SAFT are excellent in terms of duplicate and repetitive testing within 1 year. This is especially true when compared with the results of patch tests for delayed-type contact allergy. Duplicate testing with the True Test® (Kabi-Pharmacia, Uppsala, Sweden) and Finn Chambers agreed in 57% (12). In our study, the agreement between duplicate testing of SAFT varied from 88% to 100%, and thus was excellent. Statistically, the κ coefficient ranged from 0.71–0.87 in the groups with repetitive tests within 1 year. Duplicate testing with different chamber systems gave κ results varying from 0.83 – 1.00. These results are excellent.

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