

The results of skin testing with food additives and the effect of an elimination diet in chronic and recurrent urticaria and recurrent angioedema

G. MALANIN and KIRSTI KALIMO

Department of Dermatology, University of Turku, Finland

Summary

Ninety-one subjects suffering from chronic or recurrent urticaria or recurrent angioedema of 2 months to 17 yr duration were skin-prick and scratch tested with 18 various food additives. Twenty-four of the subjects (26%) had at least one histamine equivalent skin test (ST) reaction. In contrast, only 24 (10%) of 247 non-urticaria control subjects showed comparable results. An oral provocation test with food additives was carried out on 10 of the 24 ST-positive subjects with urticaria or angioedema, but only one positive reaction, caused by benzoic acid, was recorded. All 91 subjects were advised to follow an additive-free diet. The effect of the diet was investigated with a retrospective postal survey. Twenty-three ST-positive subjects returned the questionnaire, 18 had followed the diet, and 16 (89%) of these 18 had experienced marked relief of their symptoms. Correspondingly, 42 of the 47 ST-negative subjects had followed the diet, and 17 (40%) had improved. The difference was significant ($P < 0.05$). Our results suggest that skin tests with food additives can be used to measure skin hyperreactivity and that they may have a predictive value in identifying patients who will respond to an additive-free diet.

Clinical and Experimental Allergy, Vol. 19, pp. 539–543. Submitted 9 May 1988; revised 26 August 1988; accepted 14 April 1989.

Introduction

Chronic and recurrent urticaria and recurrent angioedema are common dermatological problems, and several authors have reported alleviation of symptoms during an additive-free diet [1–10], although in other reports the role of food additives has been questioned [11,12]. Oral provocation tests (OPT) with various food additives have been used to establish the causative or exacerbating agents [1–4,6–8,10–14].

Skin tests (ST) have been used to detect allergy to various foods [15–18]; skin-prick, scratch and intradermal tests with sodium bisulphite and potassium metabisulphite, two common food additives, have appeared useful in some cases [19,20]. Positive patch test results with benzoic acid have, however, shown poor correlation with OPT [21,22].

The aim of this study was to investigate the value of skin-prick and scratch tests and OPT with food additives

in subjects with chronic or recurrent urticaria and recurrent angioedema, and to find out if any correlation exists between the ST results and the effect obtained during an additive-free diet.

Subjects and methods

The study group consisted initially of 91 subjects suffering from chronic or recurrent urticaria or recurrent angioedema with a duration of 2 months or more. The physical urticarias were excluded. Two hundred and forty-seven subjects served as controls. The subjects were examined in the Department of Dermatology of Turku University Central Hospital between June 1983 and October 1986. Skin-prick and scratch tests were performed on all subjects and controls with the food additives shown in Table 1. The preservative agents were tested by the skin-prick method, and food colouring and flavouring agents and tocopherol by the skin-scratch method because of differences in the vehicle. Histamine chloride (3 mg/ml) was used as positive and physiological

Correspondence: Dr K. Kalimo, Department of Dermatology, University of Turku, Finland.

Table 1. The food additives used in the skin tests

	Concentration (%)	Vehicle
The conserving agents (scratch tests)		
Sodium benzoate	10	Water
Benzoic acid	5	Petrolatum
Sodium glutamate	10	Water
<i>p</i> -Aminobenzoic acid	5	Ethyl alcohol (70%)
Parabens (methyl-, ethyl-, propyl-, butyl- and benzyl- <i>p</i> -hydroxybenzoate, 3% each)	15	Petrolatum
Propionic acid	5	Water
Sorbic acid	2.5	Petrolatum
Citric acid	2.5	Water
Sodium metabisulphite	10	Water
Food colouring and flavouring agents and tocopherol (prick test)		
Patent blue	2.5	Water
Tetrazome orange	1	Water
Green colour*	1	Water
Poppy red†	1	Water
Chocolate brown‡	1	Water
Helioecht blau§	1	Water
E. Orange¶	1	Water
Brown colour	1	Water
Tocopherol	1	Petrolatum

* Mixture of indigo carmine and tartrazine; †, paraorange; ‡, mixture of tartrazine, indigo carmine and paraorange; §, indigo carmine; ¶, amaranth; ||, mixture of azo dyes.

saline as negative control in both tests. The tests were read at 15 min and interpreted as recommended [23]. Only weals as large or larger than that of histamine were considered positive. The subjects received information of the results. The history of salicylate intolerance and atopy was thoroughly investigated by the clinician. The subject was considered as atopic if they had or had had atopic dermatitis, allergic rhinitis or asthma or had at least one positive ST reaction with common inhalant allergens.

During the first visit the subjects had been advised to follow an additive-free exclusion diet. They were allowed to take antihistamines when needed but the usage was not recorded. At the end of 1986 all 91 subjects received a questionnaire on the diet and the occurrence of symptoms. The product groups avoided during the diet were: (1) non-steroidal anti-inflammatory drugs, (2) preservative agents, (3) beers, (4) jams, (5) candies, cakes,

cookies and ice cream, and (6) soft drinks. The observation of the diet groups was based on a subjects own notice and graded as follows: avoided completely = 3 points, almost completely = 2 points, and to some degree = 1 point. The maximum scoring was thus 18 points if the elimination was optimal.

Ten ST-positive volunteers were challenged with the food additives which had caused the positive ST result to them. The dosage of OPT was gradually increased to the approximated maximal daily intake level in Finland. The additives were in capsules which were stained opaque with titanium oxide, the solutions were given from dark bottles. At the first day the patients received only a placebo (lactose in gelatine capsules or water). The protocol was as follows: benzoic acid 10, 50, 100 and 100 mg in capsules, propionic acid 10, 50, 100 and 100 mg in 100 ml of water, patent blue 0.2, 1, 1 and 1 mg in 100 ml of water, citric acid 100 and 200 mg in capsules. The capsules or solutions were given at hourly intervals. Seven subjects were challenged with benzoic acid, five with propionic acid, two with patent blue and one with citric acid. All challenges were carried out in hospital, and on the same occasion the ST with food additives was repeated. The subjects had been symptom-free from 2 weeks to 3 yr (median 1 month) before the OPT.

The differences between the two subject groups were evaluated using the χ^2 test.

Results

Twenty-four of the 91 subjects were ST-positive with histamine equivalent weals, and 67 were ST-negative. Seventy subjects returned the questionnaire and formed the final study group. Twenty-three of them (33%) were ST-positive and 47 were ST-negative. Of the 247 control subjects 24 (10%) were ST-positive. Ten (43%) of the ST-positive subjects had suffered from recurrent angioedema and 13 (57%) had had chronic or recurrent urticaria. Eight (17%) of the ST-negative subjects had suffered from recurrent angioedema and 39 (83%) from chronic or recurrent urticaria.

ST-positive subjects

The age distribution of the 23 ST-positive subjects was 9–54 yr (mean 33 yr), 12 were females and 11 males. The duration of symptoms varied from 2 months to 16 yr (mean 4 yr 9 months). Three subjects had a history of salicylate intolerance and seven proved to be atopics.

The ST results are shown in Table 2. Four subjects reacted to more than one additive: one to patent blue, chocolate brown and helioecht blau; one to *p*-aminobenzoic acid and propionic acid; one to benzoic acid and

Table 2. The positive skin test results of 23 subjects, 11 retested, with initial and reproducible reactions indicated

	ST-positive (23 subjects) <i>n</i>	ST-positive subjects retested <i>n</i>	Reproducible reaction <i>n</i>
Benzoic acid	10	7	6
Propionic acid	8	3	3
Sorbic acid	1	0	0
Citric acid	3	0	0
<i>p</i> -Aminobenzoic acid	1	0	0
Patent blue	3	2	1
Chocolate brown	1	1	0
Helioecht blau	1	1	0
Tetrame orange	1	0	0

propionic acid; and one to benzoic acid, propionic acid and citric acid. One of the subjects with salicylate intolerance had a positive ST with benzoic acid and two others with propionic acid.

In 11 cases the tests were repeated 2 months to 3½ yr later (Table 2). A concordant result was obtained in nine subjects. Two subjects who had been positive with benzoic acid also reacted to propionic acid on the second occasion. One patent blue-positive subject was also positive with benzoic acid when re-tested. ST had become negative in two subjects, of these one had reacted to patent blue, chocolate brown and helioecht blau and the other to benzoic acid.

OPT was performed on 10 subjects with the additives which gave the positive ST results. Only one subject reacted, the agent being benzoic acid which caused reproducible itching and wealing.

Eighteen subjects had followed an additive-free diet for at least 1 month. The points scored indicating the diet observance (DO) ranged from 5 to 18 (mean 14). During the diet the symptoms had totally ceased in six subjects (33%) with a mean DO of 15 (range 10–17) and improved markedly in 10 subjects (56%) with a mean DO of 14 (range 5–18). One subject (DO=15) found some, and another (DO=14) no benefit during the diet. A striking improvement was thus observed by 16 subjects (89%). Four subjects did not follow an additive-free diet, two became free of symptoms and two had symptoms continuously. One subject gave incomplete information.

ST-negative subjects

The age distribution in this group was 10–75 yr (mean 41 yr), 34 were females and 13 males. The duration of

symptoms varied from 4 months to 17 yr (mean 3 yr 11 months). Ten subjects had a history of salicylate intolerance and 17 proved to be atopics.

Forty-two of the 47 ST-negative subjects had followed an additive-free diet (36 subjects at least for 1 month and five for about 2 weeks). The DO ranged from 4 to 18 points (mean 13 points). During the diet the symptoms had totally disappeared in three subjects (7%) with a mean DO of 16 (range 15–17). Fourteen subjects (33%) were markedly better, with a mean DO of 13 (range 6–18); this group included two subjects who only followed the diet for about 2 weeks. The symptoms improved slightly in 11 subjects, with a mean DO of 12 (range 6–17) and 14 subjects showed no change with a mean DO of 13 (range 4–18); this group included three subjects who only followed the diet for about 2 weeks. A striking improvement was thus observed by 17 subjects (40%). The proportion of subjects whose symptoms decreased during the diet was significantly greater in ST-positive than in ST-negative subjects ($P<0.05$). Five subjects did not follow an additive-free diet; one became free of symptoms while the four others had symptoms continuously.

For unknown reasons 21 subjects never returned the questionnaire. Their ages varied from 11 to 55 yr (mean 31 yr), 12 were females and nine males. One subject had a history of salicylate intolerance and five were atopics. Six of the subjects had suffered from recurrent angioedema and 15 from chronic urticaria. One of the subjects had a histamine equivalent weal with benzoic acid.

Discussion

In the literature there are not many reports of skin-prick or scratch tests with food additives. In some cases, e.g. with sodium metabisulphite, they seem to indicate IgE-mediated allergy [19,20]. On the other hand salicylate intolerance is common in urticaria patients [1–4, 6–8, 10, 13] and many of them react to food additives taken orally [1–4, 6, 10]. We wanted to study the possibility of using skin tests with food additives as predictors for this kind of hyperreactivity, especially skin-prick and scratch test methods with strict criteria for the positive skin test results.

It was evident that urticaria and angioedema subjects were more frequently ST-positives than non-urticaria controls. Among the 247 non-urticaria control subjects only 10% were ST-positive and showed histamine equivalent wealing compared with 26% from the 91 urticaria and angioedema subjects. From the study groups the subjects who presented with recurrent symptoms, especially angioedema, showed most of the skin reactions although the ages of the subjects, duration of symptoms, history of atopy or salicylate intolerance did not differ.

The additives which gave the greatest number of the ST reactions were benzoic acid and propionic acid. These reactions were also reproducible in the majority of subjects re-tested. The skin test reactions recorded represent liberation of inflammatory mediators, different food additives have various pathomechanisms to cause the wealing. Allergen dependent histamine liberation may occur [19,20]. However, the majority of the positive tests seen were caused by benzoic acid which is known to cause non-immunological reactions. According to earlier studies mediators other than histamine are involved in weal formation with benzoic acid [24,25].

The value of an additive-free diet has been questioned as a treatment modality for chronic urticaria [11,12], however, several authors have found it beneficial [1-10]. The estimation of the effect of diet is difficult because of the capricious nature of the disease and possible differences in the usage of antihistamines. In this study there may also be a bias in the results caused by the loss of 21 subjects who did not reply and also the ST-positive subjects' greater reply rate. Placebo effect or stricter observance of the diet among ST-positives is also possible as the subjects were informed of the test results. The duration of the diet required to get any effect makes it impossible to objectively follow the subject at hospital. The registration therefore depended on the subjects' own observance and announcement, which can never be absolutely reliable. The number of subjects who did not follow an additive-free diet was too small to form reliable control groups, and therefore we compared only those who had been on the diet. In this study a favourable response was particularly noticed among ST-positive subjects, with 89% experiencing a significant improvement compared to 40% of the ST-negative subjects ($P < 0.05$). There was no significant difference in the observance points between these groups and there was no strict relationship between the observance of the diet and the occurrence of symptoms. The OPT results were controversial, as documented earlier [21,22]. The test was positive only once from the 10 ST-positive subjects challenged, despite the favourable effect of the diet. Longer exposure times or other simultaneous factors would perhaps be needed to provoke the reactions.

In conclusion, the skin test models used offered an opportunity to measure the skin hyperreactivity among urticaria and angioedema patients. The skin test results also appeared to have a predictive value in identifying patients who responded to an additive-free diet. Skin tests, especially those using benzoic acid and propionic acid, may offer the possibility of studying the underlying pathomechanisms, and are therefore worth further investigations.

References

- 1 Juhlin L, Michaelsson G, Zetterstrom O. Urticaria and asthma induced by food and drug additives in patients with aspirin hypersensitivity. *J Allergy Clin Immunol* 1972; 50:92-8.
- 2 Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 1975; 93:135-44.
- 3 Ros A-M, Juhlin L, Michaelsson G. A follow-up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzoates and azo dyes. *Br J Dermatol* 1976; 95:19-24.
- 4 Warin RP, Smith RJ. Challenge test battery in chronic urticaria. *Br J Dermatol* 1976; 94:401-6.
- 5 Freedman BJ. A diet free from additives in the management of allergic diseases. *Clin Allergy* 1977; 7:417-21.
- 6 Gibson A, Clancy R. Management of chronic idiopathic urticaria by identification and exclusion of dietary factors. *Clin Allergy* 1980; 10:699-704.
- 7 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; 104:369-381.
- 8 Wutrich B, Farbo L. Acetylsalicylsäure- und Lebensmitteladditivaintoleranz bei Urticaria, Asthma bronchiale, und chronischer Rhinopathie. *Schweiz med Wschr* 1981; 111:1445-50.
- 9 Verschave A, Stevens E, Degreef H. Pseudo-allergen-free diet in chronic urticaria. *Dermatologica* 1983; 167:256-9.
- 10 Genton C, Frei PC, Pecoud A. Value of oral provocation tests to aspirin and food additives in the routine investigation of asthma and chronic urticaria. *J Allergy Clin Immunol* 1985; 76:40-5.
- 11 Kellett JK, August PJ, Beck MH. Double-blind challenge tests with food additives in chronic urticaria. *Br J Dermatol* 1984; 111:32.
- 12 Hannuksela M, Lahti A. Peroral challenge tests with food additives in urticaria and atopic dermatitis. *Int J Dermatol* 1986; 25:178-80.
- 13 Mikkelsen H, Larsen JC, Tarding F. Hypersensitivity reactions to food colours with special reference to the natural colour annatto extract (butter colour) *Arch Toxicol* 1978; Suppl 1:141-3.
- 14 Supraniam G, Warner JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986; 18:907-9.
- 15 Hannuksela M, Lahti A. Immediate reactions to fruits and vegetables. *Contact Dermatitis* 1977; 3:79-84.
- 16 Kauppinen K, Kousa M, Reunala T. Aromatic plants—a cause of severe attacks of angio-edema and urticaria. *Contact Dermatitis* 1980; 6:251-4.
- 17 Waring NP, Daul CB, deSchazo RD, McCants ML, Lehrer SB. Hypersensitivity reactions to ingested crustacea: clinical evaluation and diagnostic studies in shrimp-sensitive individuals. *J Allergy Clin Immunol* 1985; 76:440-5.
- 18 Stricker WE, Anorve-Lopez E, Reed CE. Food skin testing in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 1986; 77:516-19.

- 19 Prenner BM, Stevens JJ. Anaphylaxis after ingestion of sodium bisulphite. *Ann Allergy* 1976; 37:180-2.
- 20 Yang WH, Purchase ECR, Rivington RN. Positive skin tests and Prausnitz-Kustner reactions in metabisulphite-sensitive subjects. *J Allergy Clin Immunol* 1986; 78:443-9.
- 21 Lahti A. Non-immunologic contact urticaria. *Acta Dermatovener (Stockh)* 1980; Suppl 91:1-49.
- 22 Czarnetzki BM. *Urticaria*. Berlin: Springer-Verlag, 1986:102.
- 23 Aas K. Standardization of allergen extracts. Standardization of diagnostic work in allergy. *Clin Allergy* 1973; 3:481-2.
- 24 Lahti A, Väänänen A, Kokkonen E-L, Hannuksela M. Acetylsalicylic acid inhibits non-immunologic contact urticaria. *Contact Dermatitis* 1987; 16:133-5.
- 25 Lahti A. Terfenadine does not inhibit non-immunologic contact urticaria. *Contact Dermatitis* 1987; 16:220-3.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.