

Challenge tests with food additives and aspirin in the diagnosis of chronic urticaria

M. Kurek^{1*}, E. Grubska-Suchanek²

¹Department of Clinical Allergology. Pomeranian Academy of Medicine, Al. Powstancow Wielkopolskich 72, 70-111 Szczecin, Poland ; ²Department of Dermatology. Medical University of Gdansk, Debinki 7, 80-211 Gdansk, Poland

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Summary

We investigated 37 patients with chronic, active urticaria and histories suggestive of food and/or aspirin-related exacerbations. Medications were discontinued and all patients received a diet free of additives and common allergens for 7 days. Double-blind, placebo-controlled challenges with tartrazine, methyl-paraben, p-hydroxy-benzoate, sodium benzoate, indigotine, quinolone yellow, sodium glutamate, sodium bisulphite, and acetyl salicylic acid were performed in 18 patients who became symptom-free during the elimination diet. Skin tests with food additives were performed in all patients following the prick and patch test technique. Positive reactions to single, or multiple oral challenges were found in eight patients. In one case, positive reaction to oral challenge with sodium bisulphite was associated with a local wheal and flare skin reaction by patch testing. The discrepancy between the responsiveness to diet (n = 18) and oral challenges (n = 8) indicate that natural foods and food additives able to exacerbate an chronic urticaria are poorly understood. © 2001 Éditions scientifiques et médicales Elsevier SAS

chronic urticaria / food additives / aspirin / additive-free diet / oral challenge / patch test with sodium bisulphite

Résumé – Tests de provocations avec les additifs alimentaires et de l'aspirine dans le diagnostic de l'urticaire chronique.

Nous avons étudié 37 patients souffrant d'urticaire chronique active qui signalaient des exacerbations après l'ingestion d'aliments et/ou d'aspirine. Après l'arrêt de leur traitement, ils ont suivi sept jours de régime excluant les additifs et les allergènes alimentaires communs. Chez 18 des 37 patients devenus ainsi asymptomatiques, une provocation orale en double insu contre placebo a été effectuée avec la tartrazine, le méthyl-parabène, le p-hydroxybenzoate, le benzoate de sodium, l'indigotine, le jaune de quinoline, le glutamate de sodium, le bisulfite sodique et l'acide acétylsalicylique. Ces 18 patients ont subi aussi des prick-tests et des tests épicutanés (patch) à l'aide des additifs. Le résultat du test de provocation aux additifs et/ou à l'aspirine a été positif chez huit d'entre eux (44%). Un seul test cutané a été positif et ce avec le bisulfite sodique. Il s'agissait d'un œdème et d'un érythème local chez la malade qui réagissait au bisulfite de sodium lors de la provocation orale. La discordance entre le résultat favorable du régime d'exclusion (18 cas) et celui des provocations orales (huit cas) confirme la difficulté d'incriminer des aliments naturels et des additifs dans l'exacerbation des urticaires chroniques. © 2001 Éditions scientifiques et médicales Elsevier SAS

urticaire chronique / additifs alimentaires / aspirine / régime sans additifs / provocation orale / test épicutané avec bisulfite sodique

*Correspondence and reprints.
E-mail address: allergy@r1.pam.szczecin.pl (M. Kurek).

The first food additives used were sulphating agents. The Romans burned sulphur to produce sulphur dioxide, which was then bubbled through wine to prevent further fermentation and microbial contamination. An increase in additive intake occurred in the 19th and 20th centuries. This was related to tinned food, with a very rapid increase since the 1950s arising from fast food restaurants. Today, there are preservatives, stabilisers, conditioners, colourings, flavourings, sweeteners, antioxidants, and other natural or artificial additives used in mass-produced, pre-packed foods. The same additives (azo-, and non-azo dyes, sulphites, benzoates and parabens) are used in various drug formulations. Adverse reactions to food and drug additives are mainly non-immunologically mediated, and the mechanisms involved remain largely unknown. In 1959, Lockey first reported three patients with urticaria as a reaction to ingestion of tablets containing tartrazine [1]. Consequently, many investigators described adverse reactions to food additives, and reported that food additives might be provocative, or exacerbating factors in some cases of chronic urticaria and angioedema, or asthma and dermatitis [2-7]. The prevalence of adverse reactions to food additives has been calculated to be some between 0.01%–0.23% of the whole population, and approximately 2.0% in atopic children [8]. The prevalence has been found to be higher in studies performed with selected dyes and preservatives in patients with chronic urticaria, or asthma patients [3, 7, 9]. Despite many studies that have attempted to establish the prevalence of food additives-related exacerbations in those patients, it has often been difficult to confirm this in properly controlled challenge tests [10]. While most cases of acute urticaria can be ascribed to food allergy, this is rarely the case in chronic urticaria. Chronic, active urticaria is defined as whealing and/or angioedema lasting longer than 6 weeks and occurring at least twice a week. Although infections, adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs (NSAID), food or drugs additives, type I allergy or autoantibodies may be responsible, the eliciting factors often remain unknown. Here, we investigated the efficiencies of an additive-free diet and double-blind, placebo-controlled oral challenges with common food additives and aspirin in patients with chronic urticaria and individual histories suggestive of food and/or aspirin-related exacerbations.

PATIENTS AND METHODS

Patients

These are 37 patients with chronic, active urticaria and/or angioedema (mean age 39.6 years, range 17 to 73 years, 81% female [$n = 30$], 19% male [$n = 7$]) hospitalised from February 1997 to March 1999 in whom a standardised diagnostic and therapeutic regimen was performed. All patients reported exacerbations related to intake of particular foods (16 cases), particular foods and aspirin (six cases), unspecified foods (ten cases), unspecified foods and aspirin (two cases), aspirin only (one case), and aspirin and other drugs (two cases). The patients had a history of urticaria/angioedema between 3 months and 27 years (54% urticaria only, 30% urticaria and angioedema, 16% angioedema only). Antihistamines (astemizol was not used) and corticosteroids were stopped 7 days and 4 weeks before hospitalisation, respectively. In each case, consent for participation was obtained, and the study was approved by the Ethics Board of Medical University of Gdansk.

Evaluation of urticaria and angioedema in an individual patient

A record of visible symptoms was performed before introduction of an additive-free diet, and after oral challenges with food additives and aspirin. For quantification of symptoms, scoring proposed by Zuberbier et al. [15] was used: 0 = no symptoms, 1 = mild (< 10 wheals or an angioedema, diameter < 2 cm), 2 = moderate (disseminated, non-confluent wheals of limited extension; up to three lesions of angioedema, each < 10 cm diameter), 3 = intense (large areas of confluent wheals; diameter of angioedema > 10 cm). The evaluation of the challenge results was based on the scoring and performed when increasing doses of tested substances were given.

Laboratory tests and tests for cold-, factitious-, and cholinergic urticaria

On admission, blood, urine and stool tests were performed in all patients: total blood count and differential, ESR, electrolytes, glucose, liver enzymes, creatinine, urea, serum protein electrophoresis, thyroid antibodies, antinuclear antibodies (ANA), cryoglobulins, HBS-antigen, urinalysis and culture. Three

consecutive stool specimens were tested for eggs and parasites. In cases suspected for associated cold urticaria (one case), factitious urticaria (one case) and cholinergic urticaria (three cases), the ice cube test, test with weighted rods or exercise to the point of sweating were performed, respectively. In patients with a history suggesting chronic gastritis or gastric and/or duodenal ulcerous disease (three cases), gastroscopy followed by *Helicobacter pylori* urease test was performed. Specific IgE screening with common inhalative and food allergens (Phadiatop, F5x, Pharmacia CAP System) was performed in patients responding to the additive-free diet only.

Diet

Standardised diet was given to all patients for 7 days. These were only freshly cooked, unsulphited potatoes, polished rice, water and salt [9].

Skin tests

Skin testing was performed in patients responding to the additive-free diet. Prick and patch tests were performed for screening of type I and type IV sensitisations in all patients. For Prick test common allergens (mites, pollens, cat and dog epithels, cow's milk, egg and fish) of commercial origin (Alergopharma, Rainbeck, Germany) were used, as well as food additives (0.01 M tartrazine, 0.01 M brilliant black, 0.01 quinollone yellow, 0.2 M sodium benzoate, 0.01 M sodium bisulphite and, 0.1% methyl-paraben) obtained from Sigma, Deisenhofen, Germany. The Prick tests were performed on the volar forearm. Reactions were read at 15 minutes, and the Prick tests were assessed as positive if the wheal was ≥ 3 mm without any reaction of the negative control. As a positive control, 10 mg/mL histamine dihydrochloride was used. For patch testing, food additives 1% tartrazine, 1% brilliant black, 0.1% quinollone yellow, 3% methyl-paraben, 2% sodium benzoate and 1.0% sodium bisulphite in petrolatum, and 2.0%, 10.0% in saline were used, respectively, and were obtained from the Pharmacy of Medical University of Gdansk. The occlusion time was 48 hours. The results were read 20 minutes and 24 hours after the removal of the tested substances. To interpret the patch test, a classification of + for erythema and slight infiltration, ++ for erythema and papules, and +++ for erythema and vesicles was used [11].

Table I. Challenge schedule. Tested agents and sequential doses.

Day	Tested agents (mg)	8h00	10h00	12h00
1	Tartrazine	10	Placebo	50
2	Methyl paraben	200	Placebo	400
3	Sodium benzoate	50	200	500
4	Non-azo dyes Indigotine 10 mg Quinolone yellow 10 mg	5 + 5	Placebo	10 + 10
5	Sodium glutamate	Placebo	100	500
6	Sodium bisulphite	10	50	100
7	Acetyl salicylic acid	50	250	500

Oral challenge tests

The tested substances were applied orally in non-transparent gelatine capsules (Apipol-Farma, Myslenice, Poland) under double-blind, placebo-controlled conditions (DBPCFC). Potato starch in identical capsules was used as placebo. Placebo was given in relation 1: 4 to verum in a randomised manner (table I). All objective and subjective symptoms were recorded for 24 hours after the beginning of the challenges. The reaction was considered positive only when the original burst of urticaria/angioedema appeared (score ≥ 1). When a doubtful reaction appeared, the dose was increased if previously provided. Other questionable reactions (flare, itching, or subjective symptoms only) were retested under the same conditions. After a clearly positive reaction, no challenges were performed with other substances for the subsequent 48 hours in order to avoid testing in a period of tachyphylaxis.

RESULTS

In 37 patients involved in the study, thyroid autoantibodies were not found, and ANA were present in 19% (seven cases). Parasites (oxyuriasis) were detected in 5% (two cases). Tests for associated cold-, factitious- and cholinergic urticaria were positive in one, two and three cases, respectively. *Helicobacter pylori* infection was found in two out of three tested patients with duodenal ulcerous disease or chronic active gastritis. Except for one ANA-positive case, all the laboratory findings presented above refer to the patients not responding to the additive-free diet. Of the 37 patients tested, the symptoms disappeared

totally in 18 (48%) within 7 days on the additive-free diet. In 22% patients (four cases) who had responded to diet, Prick test and/or sIgE screening was informative. Patch testing with food additives was informative in one case only. This was a wheal and flare reaction to 1% sodium bisulphite (in petrolatum) noted after 48 hours by usual patch test. This was confirmed 1 week later with the open patch test (figure 1). Anamnestical data, results of prick and patch tests, sIgE-screening, and other laboratory findings are listed in *table II*. In 44% patients (eight cases) who had improved on additive-free diet, individual additives and/or aspirin caused objective urticaria and/or angioedema symptoms on oral challenge tests. For the most part, reactions occurred between 5 and 120 minutes, and in five cases combinations of two to four individual substances were noted. All reac-

tions resolved spontaneously within 24 hours, and these were generally mild or moderate urticaria bursts. Only one patient (No 11) developed severe angioedema with stridor, and emergency treatment with adrenaline and steroids was required (*table III*).

DISCUSSION

In contrast to genuine IgE-mediated allergy with typical symptoms strongly related to ingestion of sensitising foods, adverse reactions to food additives are difficult to diagnose. Histories are usually poorly informative. Only when additive-containing food products are incriminated, might a diagnostic additive-rich or additive-free diet be useful. If the symptoms reappear or improve significantly, a challenge test with an individual additive is the next step. Unfortunately, many of the studies based on the above principle have been criticised because of the lack of proper criteria of patient selection and exact monitoring of symptom severity, their loose definition of a positive response, and inadequate placebo controls [9, 10]. This explains different evaluations of effectiveness of additive- and salicylate-free diet (from 24 to 70%) in patients with chronic urticaria and/or angioedema [6, 9,12]. Consequently, the rate of positive reactions to multiple-additive challenges varies from 2–12%, 19%, or 31%, respectively [3, 5, 10]. We selected patients following the criterion of the history of food- and/or aspirin-related symptoms, and found that anamnestical data were generally poorly informative. In 72% of 18 patients (13 cases) who had improved on diet, exacerbation of urticaria/angioedema was related to the intake of additive-containing foods (nine cases), aspirin (two cases), and additive-containing foods or aspirin (one case). The positive response rate to challenge with individual substances was 44% (eight cases). However, the concordance of positive challenge and history suggesting a causal role of additive-containing foods and/or aspirin was found in 28% (five cases) responders only. It is known that 5–10% patients with aspirin-dependent chronic urticaria react with exacerbation after ingestion of food additives [13]. Although histories of aspirin or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity are generally quite informative, the exclusion of these factors does not obligatorily lead to remission. Therefore, it might be

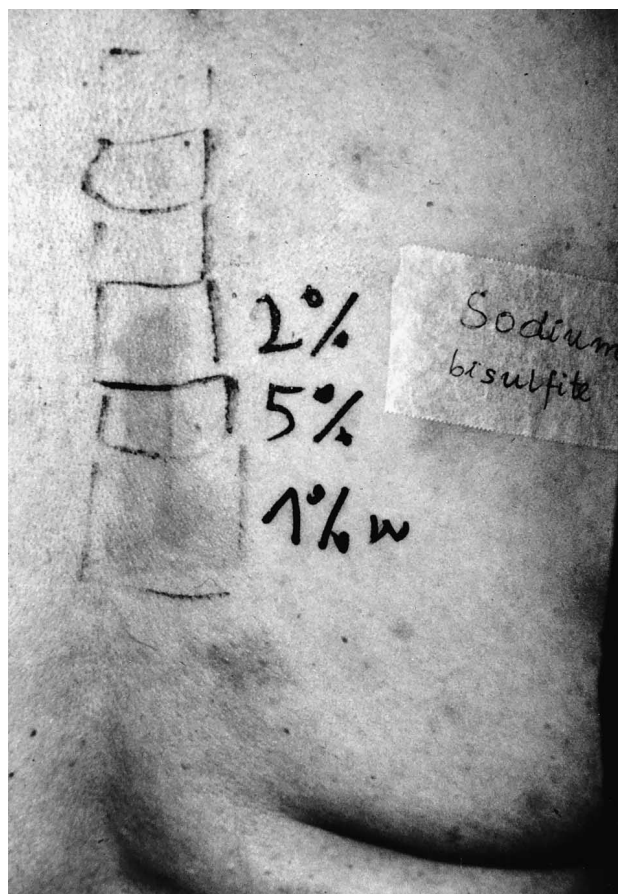


Figure 1. Wheal and erythema reactions to 2%, 5% and 1% sodium bisulphite in saline and petrolatum, respectively, in the patient with urticaria burst after oral provocation.

Table II. Anamnestical data and results of skin testing and sIgE screening in patients responding to the additive-free diet. Individual substances eliciting positive reactions by oral testing are marked.

No	Histories of food and/or aspirin-related urticaria/oedema	Skin reactions and/or sIgE when positive Atopic disease when performed	Mean score before diet introduction [2, 11, 13]	DBPCFC findings when informative
1	Unspecified legumes	<i>D. pteronyssinus</i> Pollen weeds Allergic rhinitis	2	—
2	Unspecified foods	—	2	—
3	Aspirin	—	2	—
4	Aspirin	—	2	Aspirin
5	Unspecified fruits Wine, soft drinks, tinned foods	<i>D. pteronyssinus</i> <i>D. farinae</i> , cat	1	Sodium glutamate Aspirin
6	Aspirin, egg	Egg, pollen weeds, cat food allergy	2	Sodium glutamate Aspirin
7	Unspecified food	Pollen trees, pollen grasses, pollen weeds	2	—
8	Tinned foods	—	1	Sodium benzoate
9	Tinned foods	—	2	—
10	Tinned foods Spiced foods Unspecific foods	—	2	Methyl-parabene Natrium benzoate Sodium benzoate Sodium bisulphite
11	Soft drinks, milk, aspirin	—	2	Aspirin Natrium glutamate
12	Soft drinks, smoked fish, grapes	—	2	Methyl-paraben Sodium benzoate Sodium bisulphite Tartrazine
13	Smoked meats, sausage	—	2	Aspirin
14	Soft drinks	—	2	—
15	McDonald's food, blue cheese	—	1	—
16	Instant coffee, dried fruit and nuts	—	2	—
17	Unspecific	—	2	—
18	Unspecific	—	2	—

useful to combine oral challenges with aspirin and individual food additives, the more so as oral challenges with aspirin are considered to be safer in patients with chronic urticaria than in the ones with asthma. Although we chose a very strict additive-free diet to avoid allergens, naturally occurring pharmacologically active food compounds, especially salicylates and histamine releasers, a remarkable discrepancy between responsiveness to diet and to challenges with individual substances was found. In their rigorously controlled study, Zuberbier et al. selected all available patients ($n = 64$) with chronic urticaria, and found that individual additives caused objective symptoms in nine (19%) out of 47 patients who had improved on diet [9]. These discrepancies might be related to dose dependency of involved additives,

their combined or synergistic effects with other food compounds, or existence of hitherto unknown pseudoallergens [13-15]. Following this concept, Zuberbier et al. found pseudoallergic properties of aromatic compounds of tomato in patients with chronic urticaria [16]. We found a case of positive skin reaction to sodium bisulphite which correlated to the positive result of the orally performed challenge test. Although this strongly suggests IgE-mediated sulphite hypersensitivity, this phenomenon seems to be extremely rare [10]. In patients responding to the diet, the rate of atopic diseases was 11% (two cases). This is comparable to the rate of atopic diseases in the whole population. Positive ANA (without clinical relevance, with a titer of 1:320) were detected in one case. There were no other immuno

Table III. Evaluation of urticaria/angioedema severity by score, doses of individual substances eliciting positive reactions and cumulated by oral challenge tests.

No	Mean score before diet introduction [2, 11, 13]	Substances delivering positive reactions (mg)	Doses eliciting first symptoms or positive reaction (mg)	Cumulated doses of tested substances [2, 11, 13]	Mean score after challenges	Associated subjective or objective symptoms
4	2	Aspirin	500 → 60 min	800	1	Numbness of the tongue*
		Sodium glutamate	500 → 60 min	600	1*	
5	1	Aspirin	500 → 120 min	800	1	—
		Sodium glutamate	500 → 240 min	600	1	
6	2	Aspirin	500 → 15 min	800	2	—
8	1	Sodium benzoate	500 → 240 min	750	1*	Metallic taste*
10	2	Methyl-paraben	200 → 120 min	600	2	—
		Sodium glutamate	500 → 60 min	600		
		Sodium benzoate	200 → 60 min	750	2	
		Sodium bisulphite	50 → 60 min	160	2	
					2	
11	2	Aspirin	250 → 5 min	300	3*	Laryngeal oedema*
		Sodium glutamate	500 → 60 min	600	1	
12	2	Tartrazine	50 → 360 min	60	2	—
		Methyl-paraben	400 → 240 min	600	2	
		Sodium benzoate	500 → 60 min	750	2	
		Sodium bisulphite	100 → 120 min	160	2	
13	2	Aspirin	250 → 60 min	300	2	—

logical findings suggesting autoimmunologically-mediated urticaria cases. Hypersensitivity reactions due to individual intolerances of some frequently used food additives are mostly pseudoallergic reactions. These are triggered by a variety of pathomechanisms such as: nonspecific release of mediators, hereditary or pharmacologically-induced enzyme deficiencies, interactions with the central or peripheral nervous system, or others which remain unclear [10, 15]. In Poland, labelling of food additives, following the 'E number system', has been mandatory since 1994. In their study from 1980, Rudzki et al. showed the possibility of urticaria detection with food additive intolerance by means of diet [12]. We were able to establish the responsible food additives or aspirin in 44% of the tested patients with chronic urticaria and/or angioedema only. However, a combination of additive-free diet and multiple challenge tests with individual additives including aspirin seems to be of considerable practical interest for allergists and dermatologists.

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