Value of oral provocation tests to aspirin and food additives in the routine investigation of asthma and chronic urticaria

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Nonsteroidal anti-inflammatory drugs and certain food or drug additives are known to induce acute bronchospasms, angioneurotic edema, and urticaria in susceptible patients. Thirty-four patients (17 with asthma and 17 with urticaria), whose case history suggested such intolerance, were challenged orally with increasing doses of seven compounds: acetylsalicylic acid, glafenine, sodium benzoate, sulfur dioxide, potassium sorbate, sodium glutamate, and tartrazine. Among 162 oral provocation tests, 38 were positive (20% decrease in peak flow rate or appearance of acute urticaria/angioneurotic edema). Twenty-four of the 34 patients (nine with asthma and 15 with urticaria) were intolerant to at least one compound. However, no serious reaction was observed. In 20 of these 24 patients (six with asthma and 14 with urticaria), a diet free of additives and nonsteroidal anti-inflammatory drugs resulted, within 5 days, in a marked improvement of symptoms, which persisted 8 to 14 mo after starting the diet. Age, prevalence of IgE-mediated allergy, and nasal polyposis were similar in patients with or without reactions of intolerance. Under the conditions used, oral provocation tests proved to be feasible, safe, and useful in many patients not helped by existing methods. (J ALLERGY CLIN IMMUNOL 76:40-5, 1985.)

Already recognized as early as 1902,[1] intolerant reactions to ASA such as asthma, rhinitis, urticaria, angioneurotic edema, and anaphylaxis have been often described.[2-5] Cross-reactions between ASA and NSAID are now well-known,[3, 6] and more recently numerous food additives, including dyes and preservatives such as tartrazine and sodium benzoate, have also been demonstrated to trigger the same type of reactions in patients presumed at risk for intolerant reaction.[7-10] These reactions have been termed "pseudoallergic" by some authors,[3, 7] since they truly mimic IgE-mediated allergic reactions.[2, 3, 6] Nevertheless, these reactions may occur on first exposure to the substance; the patient can react to chemically unrelated compounds.[3] So far no specific IgE has been definitely demonstrated to be responsible for the symptoms.[3, 11] None of the tests used in the diagnosis of IgE-mediated reactions (skin tests and RAST) have been observed to be of any value in the diagnosis of pseudoallergic reactions.[3, 7] Therefore, OPT with suspect compounds and subsequent exclusion diets[12, 13] have been used for this purpose with various degrees of success.[10, 14, 15]

Abbreviations used

ASA:	Acetylsalicylic acid
EIA:	Enzymoimmunoassay
NSAID:	Nonsteroidal anti-inflammatory drugs
OPT:	Oral provocation tests
PFR:	Peak flow rate
SO_2:	Sulfur dioxide

We report here the results of OPT with ASA, glafenine, and additives with a selected population of patients presumed to be at risk for intolerant reactions according to their case history and who suffered from asthma and/or urticaria/angioneurotic edema. We also compared the rate of allergic (IgE-mediated) reactions in patients with and without intolerance to ASA or food additives, and finally, we studied the effectiveness of a diet free from additives and NSAID.

MATERIAL AND METHODS

Patients

Thirty-four adult patients were studied. Seventeen patients suffered from asthma (three of them with associated urticaria), and 17 subjects suffered from chronic idiopathic urticaria and/or angioneurotic edema (thereafter mentioned as urticaria alone) for a duration of at least 3 mo. No case of acute intermittent urticaria was included. The patients

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were selected according to the following criteria: (1) a history suggesting an acute intolerant reaction to ASA or to other NSAID, (2) possible link between exacerbation of the symptoms and ingestion of food additives as noticed by the patient or by the physician, (3) failure of a usual antiallergic therapy such as environment control or immunotherapy in allergic patients (defined below), or (4) acute exacerbations of the disease without any known triggering event. None of the patients with asthma fulfilled the criteria accepted for chronic bronchitis.

Allergic investigation

In all patients a careful and detailed history was obtained by a trained allergist. All patients were skin tested by the prick method with the following antigens: pollens, house dust, mites, animal danders, molds, and food allergens (Bencard Allergy Unit, Beecham, London, U. K.). In addition, specific IgE for the corresponding allergens was assessed in all patients by a commercially available EIA test (Phadezym, Pharmacia, Uppsala, Sweden). Total serum IgE concentration was measured by use of an EIA (Phadezym IgE PRIST) of the same commercial origin. Thereafter, the patient was considered to be "allergic" if he had at least two allergen-positive results to two of the following: either history and skin tests, or history and RAST, or skin tests and RAST.

OPT

The five additives and two drugs tested in the OPT are listed in Table I. Progressively increasing doses, not higher than amounts ingested daily in a normal European diet, were chosen.[8, 16, 17] For safety reasons ASA was not tested in patients who reported intolerant reactions to this drug or to other NSAID during the last 24 mo. Also, since cross-reactivity to ASA and tartrazine has been strongly suggested by many studies,[3, 10, 18] ASA was not tested in patients with a positive OPT to tartrazine, and OPT with tartrazine was always performed before that of ASA.[6] For safety reasons patients with asthma were not tested if the PFR was lower than 70% of the predicted value.

All the compounds were obtained in a purified form (Siegfried AG, 4800 Zofingen, Switzerland) as an aqueous solution or a powder that was dissolved in 80 ml of water immediately before use. No measure was taken to mask taste or aspect of the preparation. The preparations were administered at 7 A.M. to fasting subjects, and the dose was increased every 1 to 2 hr (except for SO_2, which was increased every 30 min) until a reaction occurred. In cases of urticaria, only one substance was tested per day and at least 2 days apart. In cases of asthma, one to three substances were tested per day. OPT were performed in a single blind fashion, and a lactose placebo was administered in a random order.

Patients were requested to follow a diet free from food additives and NSAID for 14 days before the tests. Foods with high histamine or tyramine content or considered as histamine releasers were strongly restricted. The exclusion diet was established according to various recommendations[12, 16, 17] and is summarized in Table II. The prescription of the preliminary diet was considered as a necessary condition for starting OPT and for allowing the estimation of their results. In all cases considered for the study, the preliminary diet resulted in a sufficient improvement of symptoms for performing the OPT. Drugs such as theophylline and corticosteroids (doses inferior to 15 mg/day of prednisone) were maintained in some cases of asthma in which it was necessary for keeping the disease stable. The cases of urticaria could all be tested after treatment had been stopped for 14 days at least. Beta$_2$-adrenergic stimulants were stopped for at least 12 hr, and disodium cromoglycate was stopped for at least 3 days before testing.

TABLE I. Substances used in oral provocation tests

Substances	Successive doses (mg)
Lactose (placebo)	200
ASA	1, 10, 30, 50, 100, 250, 500
Glafenine*	10, 50, 200
Tartrazine	1, 5, 10, 15, 25
Sodium benzoate	10, 50, 250, 500
Potassium sorbate	10, 50, 250, 500
Sodium glutamate	1, 10, 100, 200
SO_2†	1, 10, 25, 50

*Glafenine (chloro-7-chinolyl-4-amino-2-benzoate glyceryl) is an antalgic substance used in Europe. It is unrelated to prostaglandin inhibitors.

†50, 5 mg of SO_2 in solution were obtained by dissolving 75 mg of Na metabisulfite and 75 mg of citric acid in 100 ml of water just before use.[8]

Criteria of positive tests

Broncho-obstructive response was assessed by measuring the PFR by use of a Wright minispirometer.[5, 17, 18] Measurements were performed in triplicate before and every 30 min after each challenge for 8 hr. The highest of the triplicate values was used. A test was considered positive (1) if a 20% drop in the PFR was measured at any time during the subsequent 8-hour period or (2) if angioneurotic edema/urticaria was noticed by a physician during the 18-hour period after the test. Other objective reactions such as lacrimation, running nose, and conjunctival hyperemia were considered positive only if they were associated with reactions (1) or (2).

Long-term therapeutic diet

The same additive-free diet as the one prescribed before the OPT was then used as therapeutic measure. No selective diet was prescribed in this study.

RESULTS

The mean variability of the PFR in the initial triplicate measurements, performed before OPT in all patients, was 2.8%; SD was 3.5. Eighteen of 34 patients (53%) had at least one positive OPT. In addition

TABLE II. Additive-free diet

Food permitted	
Cereals	Bread, and all cereals bought in a fresh state
Fats	Butter, olive oil
Fruits	All are permitted if in moderate amounts (ASA!)
Meats	Fresh meat; pork, eggs, and fish in only small quantities
Vegetables	All (if in fresh state) except cabbage, beans, spinach, sauerkraut; tomatoes only moderately
Condiments	Sugar, salt, pepper; others only as dried leaves; vinegar only if stated without additives
Sweets	Only homemade without additives
Beverages	Fresh milk, tea, coffee, homemade fruit juice, mineral water
To avoid	Colored toothpaste, colored cosmetics, colored beverages, wines and alcohols, artificial sweeteners, ice cream, sweets, and ready-made desserts commercially available

to the 18 patients with positive OPT, six others had a history of at least two intolerant reactions to ASA in the last few years. Therefore, as a whole, 24 of the 34 patients (71%) were considered to have intolerant reactions to at least one compound and four at the most.

Patients with urticaria were found to have intolerant reactions more often than those with asthma. Fifteen of 17 patients with urticaria (88%) and nine of 17 patients with asthma (53%) had at least one positive OPT or a history of intolerance to ASA ($p < 0.025$). Among the nine patients with intolerant reactions and asthma, three had both asthma and urticaria. Two of these three patients had at least one positive OPT with an urticarial reaction, and the third one only had a history of asthmatic reactions to ASA. Symptoms like conjunctival hyperemia, rhinorrhea, etc. were not triggered in addition to asthma and urticaria and thus did not increase the number of positive reactions.

The number of positive OPT obtained with each substance are illustrated in Table III. In patients with asthma, the positive OPT were associated with some degree of bronchospasm (mean drop of PFR 25.5% ± 2.5% [SEM]; range 20% to 34%) occurring between 3 to 40 min (mean 16 min) after the challenge. Bronchospasms usually occurred earlier after the SO_2 challenge than intolerant reactions after any other compound. The mean duration of the reaction was 1 hr 54 min (range 10 min to 8 hr). Among the patients with asthma, two who also had urticaria reacted only with urticaria, one to tartrazine, and the other to sodium benzoate. In the patients with urticaria, the positive OPT reproduced urticarian wheals, which occurred between 30 min and 17 hr (mean 4 hr 26 min) after the last challenge; the mean duration of the reaction was 12 hr 13 min (range 1 to 48 hr).

Two OPT-induced bronchospasms needed some mild therapy (salbutamol and theophylline), and 11 episodes of urticaria/angioneurotic edema received antihistamine. None of these reactions was life-threatening.

Table III, depending on the substance used, illustrates that 13% to 32% of the OPT were positive. If reactions to ASA detected by history were added to OPT results, intolerance to ASA was found in six of 17 patients with asthma (35%) and 13 of 17 patients with urticaria (76%). Six patients, whose intolerance to ASA was determined by history alone, had no positive OPT for other substances. Glafenine was tested for a possible substitute therapy in eight ASA-intolerant patients with only one positive reaction. Ten of 11 tartrazine-intolerant patients were also intolerant to ASA. Table III also illustrates that positive OPT to SO_2 were found exclusively in patients with asthma, whereas sorbate, glutamate, and glafenine triggered reactions in patients with urticaria only.

The characteristics of the patients with and without intolerance are listed in Table IV. No characteristic could be found that would discriminate between patients with and without intolerant reactions. In particular there was no significant difference between both groups in the incidence of IgE-mediated allergy that was judged by patient history, skin tests, and/or RAST. Among 24 patients with intolerant reactions, 13 were considered as "allergic"; among 10 patients (without intolerant reactions), four were "allergic." The geometric mean of total serum IgE was 78 ± 12 PRIST unit per milliliter in 24 patients with intolerant reactions and 87 ± 15 PRIST unit per milliliter in 10 patients without intolerant reactions.

A diet free of additives and NSAID resulted in clinical improvement in 20 of 24 patients with intolerant reactions and in one of 10 patients without intolerant reactions according to OPT results. The improvement occurred within 5 days after starting the

TABLE III. Cumulative numbers of positive OPT obtained with each substance

Substance	No. of tests	Number of positive tests in			
		Asthma	Urticaria	Total No.	(%)
ASA	22	0	7	7	(32)
Glafenine	8	0	1	1	(13)
Tartrazine	34	1	10	11	(32)
Sodium benzoate	33	1	5	6	(18)
Potassium sorbate	21	0	5	5	(24)
Sodium glutamate	19	0	4	4	(21)
SO_2	25	4	0	4	(16)
Total	162	6	32	38	(23)
Placebo	34	0	0	0	(0)

TABLE IV. Comparison of 24 patients* with intolerant and 10 patients with tolerant reactions

	Patients with intolerant reactions (%)		Patients with tolerant reactions (%)	
No. of cases with histories of intolerance to ASA	12	(50)	0	
M/F ratio	10/14		6/4	
Nasal polyposis	9	(37)	5	(50)
Allergic patients†	13	(54)	4	(40)
With positive history	12	(50)	3	(30)
With positive skin tests	13	(54)	4	(40)
With positive RAST	12	(50)	4	(40)
With IgE >100 PRIST unit	13	(54)	4	(40)
Age: mean; (range) in years	36	(20 to 56)	38	(17 to 54)
Disease duration: mean; (range) in years	4	(0,5 to 16)	7	(0,5 to 35)

*Eighteen patients with positive OPT and six patients with a history of intolerance to ASA are considered together.
†Defined under material and methods.

diet and persisted during a follow-up of 8 to 14 mo. Similar rates of improvement were obtained in patients with intolerant reactions and asthma (six of nine improved) and in those with urticaria (14 of 15 improved). However, only patients with urticaria (four cases) noticed complete disappearance of symptoms on the diet alone. Three of the 24 patients with intolerant reactions found the exclusion diet unfeasible, and one of them improved without diet.

DISCUSSION

Intolerant reactions to ASA and other NSAID have been reported in 1.4% to 44% of patients with asthma[3, 9, 13] and are associated with bronchial obstruction that is sometimes dramatic. Numerous studies of patients suffering from urticaria and angioneurotic edema of unknown origin have reported an incidence of 21% to 67% of patients demonstrating reactions to NSAID and food additives. The beneficial effect of additive-free diets has also been reported by several authors.[3, 12, 14] There is therefore a definite need for a practical, reliable, and safe test allowing such patients to be recognized. Under the conditions used in our study, OPT fulfilled these criteria since (1) they gave a high yield of positive results, (2) they did not cause dangerous patient reactions, and (3) they led to a successful therapy in many patients.

The high proportion of patients with positive OPT in the present study (71%) is probably linked to the selection of cases based on a history suggestive of intolerance to NSAID or food additives. The incidence of reactions to ASA, estimated at 0.9%[3] in an unselected population, is much higher in selected patients and is known to correlate with OPT of other NSAID and food additives.[5, 8, 10] Therefore, in patients suffering from asthma and urticaria, NSAID should be ad-

ministered with the greatest caution. In our study glafenine was found to be harmless in most patients with ASA-intolerance and can be an alternative in these cases.[4, 6]

The high yield of positive results in our OPT is perhaps also the result of the choice of the compounds tested. ASA, tartrazine, and sodium benzoate elicited the highest incidence of positive results in both asthma and urticaria.[7, 8, 10] These data were confirmed here. Our results demonstrated cross-reactivity between tartrazine and ASA, as in other studies,[8, 10, 14] although intolerance to tartrazine may exist without intolerance to ASA.[3, 4] The clinical relevance of this finding could be high since a survey of 634 common pharmaceutical preparations in Switzerland revealed the presence of tartrazine and sodium benzoate in, respectively, 68 (10.7%) and 70 (11%) preparations.* The presence of these two compounds is also legally tolerated in a large number of commercially available foodstuffs.[16]

In our study sorbate and glutamate triggered only urticarial reactions. The highest dose of glutamate tested was 200 mg since 200 to 300 mg may be ingested per day in a regular diet. However, 2 to 5 gm of glutamate can occasionally be ingested in Chinese meals causing serious asthma reactions, sometimes referred to as "the Chinese restaurant asthma."[19] Unlike the two previous substances, SO_2 was found to trigger exclusively broncho-obstructive responses, thus suggesting that this air pollutant, which is also found in wine, grape juice, or vinegar[16, 17] (in the same amount as that used in our study), can be harmful for patients with asthma[20, 21] through oral administration.

In spite of this high rate of positive results, no severe reaction was registered during our 162 tests. The absence of serious reactions might be due to a careful selection of patients, the compounds tested, and the doses used. Patients known to be intolerant to ASA were not tested with this drug because reactions to NSAID can be life-threatening.[3, 6] Also, those who had a positive OPT with tartrazine were not tested with ASA since cross-reactivity between these two compounds has been suggested.[7, 8, 10] The initial doses of each additive were lower than those ingested in a normal diet.

The usefulness of finding positive OPT is suggested by the improvement reported after excluding NSAID and food additives from the diet. Our success rate is comparable to that of other authors.[3, 12, 14] We believe that the improvement obtained can actually be ascribed to the diet, despite the absence of a control group, because it happened within 1 to 5 days after starting the diet in patients having experienced multiple therapeutic failures in the past and because it was still present 1 yr after starting the diet.

Improvement under the exclusion diet before the OPT and also the absence of acute variation of disease during the OPT period was found to be a necessary prerequisite for the interpretation of the results. Since the pretest diet was often successful, one could argue that it could replace OPT and also be diagnostic. However, the finding of positive tests could help to convince the patient of the usefulness of the diet.

OPT are unfortunately time-consuming and need good cooperation from the patient and prolonged medical supervision. However, they were generally well accepted in our study, especially by patients suffering from chronic urticaria or asthma with many previous unsuccessful investigations and treatments.

It is understandable that patients improved in the course of the preliminary diet can, however, subsequently react negatively in the tests, since the diet was free of many more additives than those compounds tested.

Originally, intolerance to ASA has been described mostly in adult subjects with asthma with a high prevalence of nasal polyposis and a low prevalence of allergic (IgE-mediated) reactions.[2, 3] However, when patients with and without intolerant reactions were compared in our study, we, like others,[5, 13, 15] could not find any clinical characteristic that was specific to patients with intolerant reactions. The mean age and prevalence of nasal polyposis were similar in both groups. More interestingly, there was no difference in the prevalence of IgE-mediated allergy, as defined by rather restrictive criteria. Thus, it appears that allergic and pseudoallergic mechanisms often coexist and consequently should both be investigated.[5, 15, 18]

The appearance of urticaria after glutamate challenge in four patients is also interesting because this substance was rather known for triggering asthma. In these cases the skin lesions appeared 1, 2, 6, and 6 hr, respectively, after challenge with 5, 200, 10, and 100 mg, respectively, of sodium glutamate.

In conclusion, under the conditions used, OPT have proved to be feasible, safe, and useful in the routine investigation of asthma and urticaria. OPT elicited a high yield of positive results in selected cases. They led to successful therapy in several patients suffering from chronic asthma and urticaria who had not been helped by other diagnostic methods and treatments so far available.

*Genton C: Unpublished data.

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