

Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity

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Seven of 8 recently investigated aspirin-sensitive patients reacted with asthma, urticaria, or both after 1 to 2 mg. of the azobenzene dye, tartrazine. Tartrazine is commonly used as a food and drug color and a daily intake of several milligrams is possible. The patients also reacted to some benzoic acid derivatives. All of these food-and-drug additives may be difficult to avoid. It is important, therefore, that they are properly identified since they are dangerous for certain patients with asthma and urticaria. Administration of these drugs to patients with a history of reactivity is a procedure of considerable danger that should be done only with extreme caution and informed consent.

It is well known that many patients with bronchial asthma and chronic urticaria show a pronounced hypersensitivity to aspirin, sometimes leading to fatal reactions. There is evidence that the effect of aspirin becomes apparent only when several factors are present at the same time.^{1, 5} Various hypotheses have been presented for the mechanism of the reactions to aspirin. In some patients the clinical symptoms are of an anaphylactic type and suggest an allergic pathogenesis. Acetylated proteins² or aspirin anhydride impurities³ have been proposed as possible antigens. Yurchak and associates⁴ have found no conclusive evidence of specific immunological reactions. The fact that not only aspirin but also other chemically different compounds, such as indomethacin, antipyrine, and tartrazine can precipitate attacks might suggest a non-allergic mechanism. Alternative explanations along this line include the theory of an alteration of kinin receptors in the lungs and the capillaries as proposed by Samter and Beers.^{5, 6} Direct activation of the complement system or lack of an inhibitor to an enzymatic reaction are 2 other possibilities discussed by Yurchak and associates.⁴

We have studied patients with aspirin hypersensitivity for some time, but only recently have we become aware of the importance of the associated sensitivity to the yellow azobenzene dye, tartrazine. This dye is commonly used, and it is an approved food-and-drug additive. Asthma and urticaria caused by tartrazine

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was first described by Lockey.⁷ Since then 18 such patients and one case of tartrazine-induced purpura have been described.^{6, 8-11} Samter and Beers⁸ found a reaction to tartrazine in 3 out of 40 aspirin-sensitive patients. During the last few months we have been able to demonstrate a pronounced tartrazine hypersensitivity in 7 out of 8 of our aspirin-sensitive patients. We have also found an associated reaction to benzoates in some patients. This, and the surprisingly high number of foods and drugs which contain tartrazine as well as other additives, have prompted the following preliminary report. The administration of these drugs to patients with a history of reactivity is a potentially dangerous procedure that is not recommended for general use.

MATERIAL AND METHODS

Compounds used

The dye tartrazine, (FDC Yellow No. 5), was dissolved in water and given orally with 10 to 20 ml. of water. The initial test dose was 1 mg. except in one case in which 0.75 mg. was given.

The following drugs were administered in colorless gelatin capsules with lactose to complete to filling of the capsule. No other additives besides lactose were used: (1) acetylsalicylic acid* (aspirin), capsules with 1, 2.5, 5, 10, 50, and 500 mg. were available; (2) purified acetylsalicylic acid† (free from the anhydrides) in amounts of 1, 2.5, 5, 10, 50, 100, 250, and 500 mg. per capsule; (3) acetylsalicylic acid anhydride‡ in capsules containing doses of 5, 10, 25, and 100 mg.; (4) 2-hydroxybenzyl alcohol (Saligenin),‡ 50 mg. per capsule; (5) 4-hydroxybenzoic acid,‡ 50 mg. per capsule; (6) benzoic acid sodium salt,‡ 250 mg. per capsule; (7) Lactose in 100 mg. dose was used as a placebo.

Testing procedure

The provocation tests were done when the patients were as free as possible from their symptoms. As a rule, other drugs were not used during the 3 days preceding the provocation test which was made in the morning after a light breakfast. The patients, all of whom were known from previous tests or history to react to aspirin, were informed that various products which might be present in food and drugs were to be tested. The amount or type of drug was unknown to them. We usually started with benzoate and its derivatives. The minimal dose of purified acetylsalicylic acid which gave symptoms was determined in the last provocation tests. The day of the placebo varied. The initial dose of acetylsalicylic acid was usually 50 mg. in patients with urticaria as the dominating symptom and 1 mg. in those with mainly or only asthma. If no response or only an uncertain one occurred within one hour, the dose was increased. Sodium benzoate was given in an initial dose of 250 mg. After 2 hours another 250 mg. was given if no reaction occurred. A single dose of 50 mg. of hydroxybenzoic acid and hydroxybenzyl alcohol was used except in 2 patients who were given another 50 mg. of hydroxybenzoic acid. Only one type of drug was tested per day and a new test with another drug was not made until the previous reaction had disappeared.

CASE REPORTS

Case 1

A 24-year-old man had urticaria which began after he had taken 0.5 Gm. of aspirin for a hangover. He discontinued the use of aspirin and used an antihistamine, clemastine, 3 times daily for one month without any effect. He was then admitted to the hospital where a medical

*Bofors AB, Molndal, Sweden.

†Kindly supplied by Prof. H. L. Vogel, Chemische Fabrik, Aubing, Munich, Germany.

‡Sigma Chemical Company, St. Louis, Mo., U.S.A.

TABLE I. Reactions in 7 aspirin-sensitive patients to tartrazine, salicylates, and benzoates: Testing hour

Substance	Patient 1	Patient 2	Patient 3
Aspirin	500 mg., moderate angioedema and urticaria	100 mg., severe angioedema and urticaria	Not done
Acetylsalicylic acid without its anhydride	Not done	50 mg., severe angioedema and urticaria	3.5 mg., severe asthma and urticaria
Acetylsalicylic acid anhydride	125 mg., no reaction	Not done	15 mg., rhinitis and asthma
2-Hydroxybenzyl alcohol	50 mg., moderate urticaria	50 mg., moderate angioedema and urticaria	50 mg., severe asthma
4-Hydroxybenzoic acid	50 mg., slight urticaria	50 mg., moderate angioedema and urticaria	100 mg., slight asthma
Sodium benzoate	500 mg., no reaction	500 mg., no reaction	500 mg., slight asthma
Tartrazine	1 mg., severe urticaria	2 mg., facial erythema and urticaria	1.5 mg., severe asthma lasting four days
Placebo	No reaction	No reaction	No reaction

*Sodium salicylate 500 mg. (free from anhydride) provoked rhinitis, asthma, and urticaria.

†A repeated test with 10 mg. showed more pronounced symptoms and general malaise.

examination revealed nothing abnormal except urticaria. His urticaria ceased 3 days after he stopped taking the antihistamine.

In the provocation tests (Table I) tartrazine produced a much more intense urticaria within one hour than any of the other chemicals. It was also revealed that the antihistamine with which he had been treated contained 30 μ g of tartrazine per tablet.

The patient was told to avoid drugs and, as far as possible, food additives. Since then he has not had any symptoms of urticaria.

Case 2

A 54-year-old woman has had a disabling urticaria and angioneurotic edema since 1969 and bronchial asthma since 1970. In 1970 she developed a severe attack of urticaria and angio-edema after taking aspirin. She has been hospitalized for several months mainly for her urticaria and has been unable to work for long periods. In the summer of 1970 she had a period with only minor symptoms of urticaria and asthma. In the following autumn she started to take a new β -receptor-stimulating drug for her asthma. It had no effect on her asthmatic symptoms and after 1 to 2 weeks of treatment she had a relapse of her urticaria. A connection with the drug was suspected and its administration was discontinued. A number of drugs were then tried for treatment of her urticaria without any success. Finally she obtained some relief from an antihistamine which we now know is free from dye additives.

Provocation tests with aspirin, hydroxybenzyl alcohol, hydroxybenzoic acid, and tartrazine induced urticaria and facial erythema within one hour (Table I). She also complained of a feeling of tightness in her chest for one hour but had no rhonchi. The reaction to tartrazine might explain much of her persistent urticaria since several of the drugs given earlier to this patient contained up to 2 mg. of tartrazine per tablet. The relapse in the autumn of 1970 could certainly be caused by the new asthma drug as the ordinary daily dose of that drug contained 1.2 mg. of tartrazine. During the last few months the patient has been kept on a diet in which we have tried to avoid all food, drinks, and drugs containing dyes, salicylates, and benzoates. She has had only minor asthmatic symptoms and is practically free from urticaria.

was begun with a small dose and increased 2 to 10 times if no reaction developed within one

Patient 4	Patient 5	Patient 6	Patient 7
Not done	500 mg., angio- edema and urticaria	500 mg., angio- edema	Not done*
4.5 mg., severe asthma and rhinitis	Not done	Not done	Not done*
10 mg., no reaction	Not done	25 mg., no reaction	Not done
50 mg., no reaction	50 mg., itching and urticaria	50 mg., itching and urticaria	Not done
50 mg., moderate asthma, rhinitis and itching	50 mg., angio- edema and urticaria	100 mg., itching, urticaria and malaise	50 mg., asthma and severe urticaria
500 mg., no reaction	500 mg., pharyngeal edema and urticaria	500 mg., no reaction	250 mg., asthma and urticaria
1 mg., slight asthma; 5 mg., severe asthma	1 mg., facial flushing, itching and urticaria†	1.5 mg., swelling of pharynx, urticaria and malaise†	1 mg., rhinitis, dyspnea; 5 mg., also severe urticaria
No reaction	No reaction	No reaction	No reaction

Case 3

A 17-year-old girl had a history of nasal polyps and bronchial asthma which began at the age of 6. Her asthma has been of chronic character with many exacerbations which have required hospitalization. She has also suffered from itching, increased dermatographism, and urticaria. She had had a pronounced hypersensitivity to aspirin for 3 years and had also noticed that apple juice, broccoli, dill pickles and bananas may possibly increase her symptoms. Allergologic investigation, as well as a radioallergosorbent test (RAST), have not revealed any atopic allergy.

Provocation tests caused hypersensitivity reactions of rhinitis and asthma within 10 to 60 minutes to all drugs except the placebo. In addition, urticaria and a further increase of her dermatographism occurred at the same time following the administration of purified acetylsalicylic acid (Table I). The reactions were most pronounced after the administration of purified acetylsalicylic acid, 2-hydroxybenzyl alcohol, and tartrazine. Administration of epinephrine was needed to stop the attacks.

Case 4

A 29-year-old woman had nasal polyps and "bronchitis" which began at the age of 8. The first severe asthma attack occurred at the age of 12 when she took an aspirin tablet for the first time. Since then she has always had nasal swelling and moderate to severe asthma of a non-atopic character. Frequent respiratory infections often increased her asthmatic symptoms. The patient had negative skin tests to common allergens.

In November, 1971, she came to the hospital as an emergency case with an acute asthma attack precipitated by an ampicillin tablet. A RAST test to penicilloyl and an intracutaneous test to benzil-penicillin were negative as well as an oral provocation test with 0.6 Gm. of tartrazine-free ampicillin. Since the ampicillin tablet contained 0.2 mg. of tartrazine and provocation tests with tartrazine produced asthma (Table I), it seems probable that her attack was caused by tartrazine. The patient also remembers having an attack of asthma after taking a yellow C-vitamin drink (which contains tartrazine) and eating mayonnaise. She also used a contraceptive pill which contained 0.1 mg. of tartrazine.

Tests with purified acetylsalicylic acid and tartrazine produced severe asthma. Within a half hour after 4-hydroxybenzoic acid she developed moderate asthma, rhinitis, and itching. Epinephrine was given to interrupt the reaction.

Case 5

A 47-year-old woman had migraine since childhood and recurrent urticaria for 40 years. She has detected that she vomits and has severe urticaria after taking aspirin. Beets, canned peas, and coffee also produce symptoms. Provocation tests were positive to benzoates and tartrazine. Flushing and itching were evident after approximately 30 minutes, whereas the urticaria was most evident after 6 to 12 hours. Since she has maintained a diet which is free from benzoates, she has scarcely any symptoms of urticaria.

Case 6

A 57-year-old woman with periods of asthma since the age of 17 had recurrent urticaria for the past 7 years. For many years she has suffered constantly from swollen nasal mucosa. She has a feeling of heaviness, tightness of the head, and general malaise before the onset of urticaria and asthma. She suspected an intolerance to lingonberry jam, "soft drinks," and some yellowish-colored buns. She rarely used aspirin and was not aware of any hypersensitivity to that drug.

At the time of testing she had been free from asthma for about one month and from urticaria for one week. One hour after the provocation test with aspirin angio-edema, increased nasal swelling, headache, and dyspnea developed, but no real asthma was noticeable. The patient complained of headache, malaise, sore and swollen throat, and increased dyspnea about one hour after provocation tests with benzoates and tartrazine. After 2 to 3 hours she had developed pronounced urticaria. Repeated tests were performed with tartrazine and they always induced the same reaction.

Case 7

A 49-year-old woman had pulmonary tuberculosis from 1945 to 1954 and was treated with para-amino salicylic acid. Perhaps it is coincidental, but from approximately that time she has also suffered from nasal congestion and complained about an asthma-like bronchitis. There has been a pronounced increase of her asthma during the last 5 years and she also developed symptoms of severe urticaria. She has not been aware of any precipitating factors but has consumed fresh and preserved fruits and berries daily since 1966 at which time she had moved to a house with a large fruit garden.

The provocation tests with 500 mg. of sodium salicylate induced nasal congestion, headache, sweating, rhinitis, and asthma within one hour and urticaria within 2 to 3 hours. The urticaria was most pronounced after 6 to 12 hours. She also reacted in the same way with asthma and urticaria after the administration of sodium benzoate and 4-hydroxybenzoic acid. These tests were repeated one month later with the same results. A 1 mg. dose of tartrazine induced rhinitis and dyspnea. When an additional dose of 5 mg. was given, the patient also developed urticaria. The patient has improved after being kept on a diet in which dyes and preservatives are avoided.

DISCUSSION

Samter and Beers⁶ followed 182 aspirin-sensitive patients with asthma, and sometimes also urticaria, and found associated sensitivities to foods and drugs in 42. Fourteen patients (< 8 per cent) were sensitive to tartrazine. However, it is not obvious from that study if provocation tests had been made in all patients and, if so, whether the doses required were sufficient to induce symptoms. Samter and Beers described in another study⁵ 40 aspirin-sensitive patients of whom 3 reacted to 25 mg. of tartrazine. Thus, one has the impression that the frequency

of tartrazine reactions is fairly low among patients sensitive to aspirin. Our finding that 7 out of 8 of the aspirin-sensitive patients in our latest study are highly sensitive to even 1 mg. of tartrazine has made us re-evaluate the importance of this approved food additive. Why they also react to tartrazine is unknown. Tartrazine taken orally undergoes an azo-reductive cleavage in the gut. In man it is completely excreted as sulfanilic acid within 48 hours.¹²

The level of sensitivity to aspirin and tartrazine may vary from time to time. If Samter and Beers^{5, 6} tested the patients when they were in a phase of decreased sensitivity, it could possibly explain the lower incidence of reactions to tartrazine. We therefore think that, although repeated provocation tests involve a considerable risk for severe reactions, they should be undertaken because patients may obtain considerable relief when they are put on a suitable diet and drug regimen.

Cross-sensitivity to benzoates seems to be uncommon.¹³ The only case we have found described is that of Chafee and Settippene⁸ in which benzoates are shown to probably cause a reaction. The doses used in the provocation tests may seem to be high but this amount can easily be obtained merely by unknowingly consuming certain types of preserved foods or beverages which contain up to 1 to 2 Gm. of benzoates per 1,000 Gm. A hypersensitivity reaction to 4-hydroxybenzoic acid was seen in all of our patients, whereas only 3 patients reacted to sodium benzoate when given it in a 5 to 10 times larger dose. Why the hydroxy compounds tested are more reactive needs further investigation.

The presence of the immunogenic substance, acetylsalicylic acid anhydride, in commercially available aspirin has been shown by de Weck.³ He proposed that the anhydride might be responsible for some of the untoward reactions to aspirin. In one of our patients it produced rhinitis and asthma within 30 minutes. However, this might be due to the formation of acetylsalicylic acid to which the patient is highly sensitive, reacting severely to only 3.5 mg. Acetylation of proteins has been regarded as another possible mechanism.² It does not, however, seem to be involved in our patients who reacted to several nonacetylated substances.

When looking at the clinical symptoms of our patients we find that 4 of the 6 patients with urticaria also have asthma. Two of them reacted in the provocation tests with both asthma and urticaria, whereas 2 showed angio-edema and urticaria but no real asthma, although one complained of tightness of the chest. The reason might be that in the period before the testing, urticaria had been the prevailing symptom. One of our patients (Case 4) who had no history of urticaria reacted with asthma but also complained of itching with hydroxybenzoic acid. It therefore seems obvious that the dominating symptom is reproduced in the provocation tests. The doses of acetylsalicylic acid needed to produce a reaction in the 2 patients with mainly asthma and nasal polyps (Cases 3 and 4) were much lower than in the others. It is uncertain whether or not they represent a different type of aspirin hypersensitivity with a mechanism for reactions separate from those present in the other patients.

We have also been alarmed to find how often considerable amounts of tartrazine, as well as several other additives such as benzoates, are used without any information being available to the prescriber and consumer. Feingold¹⁴ discusses

the use of over 2,700 food additives which have been compiled and classified by the National Research Council, and Lockey¹¹ has recently exemplified the great number of various additives present in some common drugs. The problems associated with food and drug dyes in an asthma patient sensitive to aspirin, sodium benzoate, and tartrazine have been analyzed by Chafee and Settippane.⁷ They also discussed cross-reactions between chemically related red, yellow, and blue colors. Detailed declarations of additives in foods and drugs are therefore highly desirable.

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