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A follow-up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzoates and azo dyes

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SUMMARY

We have studied seventy-five patients with recurrent urticaria and angio-oedema of more than 4 months duration and with positive provocation tests to aspirin, azo dyes, and/or benzoates. Cross-reactions between the test compounds were common. The patients were recommended to be on a diet free from salicylates, benzoates, and azo dyes. They were then followed for 6–24 months. At the follow-up, 24% were free from symptoms, 57% considered themselves much better and 19% stated that they were slightly better or unchanged. All patients had followed the diet for at least 1–3 months. Most of those who became totally free of symptoms did not continue with the diet, while most of the patients who considered themselves much better found that it was necessary to continue on the recommended diet. They usually developed symptoms as soon as they ingested something containing azo dyes or benzoates. To be able to maintain such a diet, it is important that the content of additives in food and drugs be properly declared.

Benzoates and azo dyes are commonly used as additives in food and drugs. These compounds, as well as aspirin, are often responsible for flare-ups in patients with recurrent urticaria (Michaëlsson & Juhlin, 1973). The mechanism for this hypersensitivity is obscure and no evidence for an antigen–antibody mediated reaction has been found (see Warin & Champion, 1974). Provocation tests that precipitate an urticarial reaction are still the only way to establish the hypersensitivity. Patients with positive reactions have been asked to try to follow a diet free from these substances. In order to determine to what extent they improve on such a regimen, a follow-up study has been done on seventy-five patients, who, 6 months–2 years previously, had one or several positive provocations to tests with aspirin, benzoates and/or azo dyes.

METHODS

Patients

The study included 24 men and 51 women between the ages of 14 and 66 years with one or several positive provocation tests to aspirin, benzoates, or azo dyes. They represent 68% of all patients with

chronic urticaria studied during this period. Twenty-one had symptoms of recurrent urticaria and fifty-four had urticaria and recurrent angio-oedema periodically or continuously for at least 4 months. The frequency of symptoms was noted both before the provocation tests and at follow-up after 6–24 months. The patients were asked whether they had observed any flare-up of urticaria after taking aspirin or after ingestion of food known to contain a high content of preservatives and/or dyes. None had physical urticaria or any evident allergic urticaria. Eight of the patients also had bronchial asthma and five had thyroid disorders that were being treated with l-thyroxine. One patient had diabetes mellitus, one had pernicious anaemia, one hyperparathyroidism, and one systemic lupus erythematous. The patients were otherwise healthy. They had previously been treated with different antihistamines, mostly without any obvious improvement.

The provocation tests have previously been described in detail (Michaëlsson & Juhlin, 1973). The patients were admitted to the hospital and were given a diet free from dyes and preservatives. Those who had frequent recurrences of urticaria often had been on such a diet even before being admitted. The provocation tests were performed when the patients had slight or no symptoms of urticaria. Antihistamines or steroids were not allowed. As a positive provocation, only objective signs occurring within 20 h were accepted, i.e. urticaria, angio-oedema, rhinitis, sneezing, or hoarseness. Subjective symptoms such as itchy skin, headache, breathing difficulties, etc. were recorded but not accepted as a positive provocation.

The following compounds and doses were routinely tested: Placebo = lactose or starch (100 mg), aspirin (1, 5, 10, 50, 500, 1000 mg), 4-hydroxybenzoic acid (50, 100 mg), sodium benzoate (50, 250, 500 mg), and the azo dyes, tartrazine, New Coccine, and Sunset Yellow (1, 2, 5, 10 mg). Patients with a history of asthma started with 0·1 mg of aspirin or dye. After a light breakfast, the substance to be tested was given in the lowest dose at 8 a.m. If no objective reaction could be noted, additional and increased doses were given at 1 h intervals. Only one substance was given per day. The tests which were questionable and difficult to interpret were repeated on another day. The order of the tests varied but placebo was usually given at the beginning and aspirin at the end.

The patients were interviewed 6 months–2 years after the provocation tests. During this time they had been asked to follow a diet that was free from dyes and benzoates as far as possible and to avoid drugs containing aspirin and those that were coloured. They had been given written general instructions with concrete examples about what to eat and what to avoid (see Michaëlsson & Juhlin, 1973).

RESULTS

Provocation tests

The types of drugs giving positive reactions are shown in Table 1. Twelve of the patients tested were positive only to aspirin, two patients only to benzoates, and seven patients only to azo dyes. Positive provocations to several compounds were common. Those who were positive to aspirin often also reacted to the other compounds. Sixteen patients were negative to aspirin but positive to benzoates and/or azo dyes. Provocations with the placebo were not done with two patients but were negative in the other seventy-three patients.

Twenty-seven of the fifty-nine patients with positive aspirin provocation had previously observed a flare-up of urticaria after taking aspirin (Table 1). One patient with a history of hypersensitivity to aspirin had a negative aspirin provocation test.

Thirteen of the sixty-three patients with positive provocations to benzoates and/or azo dyes had a positive history to these compounds. Three patients with a history of reaction to preservatives and/or dyes had negative provocations to these compounds but were positive to aspirin.

Nineteen per cent of the patients with only one positive provocation had a history of hypersensitivity, whereas 54% of those with more than one had such a history.

TABLE 1. Number of patients with positive provocations and a history of hypersensitivity to aspirin, benzoates, and azo dyes

Substance	Positive provocations	History of hypersensitivity: Aspirin	History of hypersensitivity: Benzoates and azo dyes
Aspirin only	12	3	0
Benzoates only	2	0	0
Azo dyes only	7	0	1
Benzoates + azo dyes	7	0	3
Aspirin + benzoates	11	7	1
Aspirin + azo dyes	12	7	3
Aspirin + benzoates + azo dyes	24	10	5
Totals	75	27	13

Follow-up study

All of the seventy-five patients were interviewed after 6–24 months. The patient's record of the number of days when urticaria occurred (daily, a few times a week, or 1–4 times per month) during the month prior to admission to hospital for provocations is compared with the corresponding figure for the month before the follow-up (Fig. 1). Forty-nine patients were completely free from urticaria or had urticaria less frequently compared with the previous hospital admission, while eight patients had urticaria more frequently. It should be pointed out that here only the frequency of urticaria is recorded. The intensity of the symptoms and the number of lesions are evaluated when the patients give their opinion of the changes in their condition after the diet (Table 2). Of the seventy-five patients, eighteen had

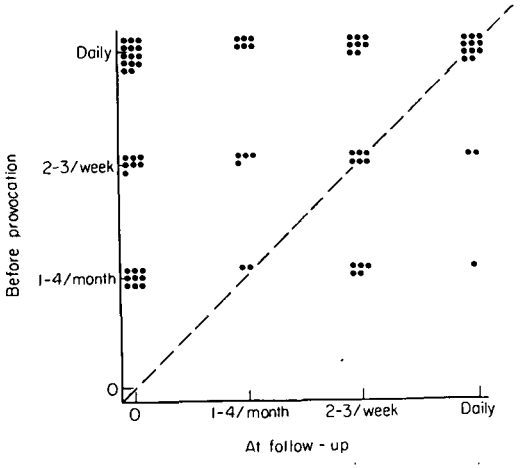

FIGURE 1. Frequency of attacks with urticarial lesions during the month prior to provocation tests and the follow-up after 6–24 months. Frequencies are based on the patient's statement of approximate number of days with urticaria. Each dot represents a patient.

TABLE 2. Follow-up study of seventy-five patients with chronic urticaria in relation to diet maintenance

Patient's opinion of urticaria status	Diet 1–3 months	Maintains diet	Totals
Symptom-free	13	5	18
Much better	11	32	43
Slightly better or unchanged	3	11	14
Totals	27	48	75

TABLE 3. Status at follow-up and number of types of compounds (aspirin, azo dyes, benzoates) giving positive provocations

Patients' opinions of urticaria status	No. of types			Totals
	1	2	3	
Sympton-free	7	8	3	18
Much better	12	18	13	43
Slightly better or unchanged	2	4	8	14
Totals	21	30	24	75

TABLE 4. Duration and improvement of urticaria

Duration of urticaria (years)	Free from symptoms	Much better	Slightly better/ unchanged	Totals
$<\frac{1}{2}$	10	9	3	22
$\frac{1}{2}$–1	1	7	2	10
1–5	2	15	6	23
>5	5	12	3	20
Totals	18	43	14	75

been free from urticaria for at least 6 months and forty-three patients considered themselves much better. Fourteen patients thought that they were either slightly better or unchanged.

The diet was followed for at least 1–3 months by all patients and forty-eight were still on it at follow-up. One of the eighteen patients who were free from urticaria for 6 months still followed the diet since he dared not give it up. Four others who were symptomless had a modified diet and avoided aspirin and certain products with a high content of dyes or benzoates.

Thirty-two of the forty-three patients who considered themselves 'much better' still followed the diet and their urticaria worsened if they failed to do so. The eleven patients of the forty-three who had followed the diet only for a short time did not consider the diet of any significance with regard to their urticarial symptoms but some avoided aspirin and strongly coloured products.

Fourteen patients were unchanged and eleven of them still followed the diet; several of them became worse if they did not.

In Table 3 the follow-up status of the patients has been correlated with the number of types of compound giving positive provocations (aspirin, benzoates, or azo dyes). Of the eighteen patients free from urticaria, seven had positive provocation to only one compound and three were positive to three types. Among the fourteen patients who were unchanged or slightly better, two were positive to one compound and eight to three.

The duration of urticaria in the seventy-five patients was over 5 years in twenty patients and five of them were symptom-free at follow-up (Table 4). Twenty-two patients had suffered from urticaria for less than a year and eleven of these were symptom-free at follow-up.

COMMENT

Fifty-five per cent of all our patients with chronic urticaria and 84% of those with positive provocation tests had reactions to aspirin; however, only about half of those reacting knew that they had such a hypersensitivity. Similar figures for reactions to aspirin and food additives in patients with bronchial asthma have been found by Rosenhall & Zetterström (1974). Our figures concerning reactions to aspirin are somewhat higher than those reported in the literature, where an exacerbation was noted after aspirin challenge in 41% of the patients with chronic urticaria (James & Warin, 1970) and where a positive history was found in about 22% of them (Moore-Robinson & Warin, 1967; Champion *et al.*, 1969). Lower figures for reactions to tartrazine (13–25%) and benzoates (11–40%) have been reported by others (Doeglas, 1975; Warin & Smith, 1976; Thune & Granholt, 1976). The reason for the higher figures in our patients might be due to the fact that they were not given any antihistamines and the

possibility that they were in a more active phase of their disease. In addition to tartrazine, we also tested two other azo dyes and the enlarged azo group may have yielded a higher percentage of positive reactions. Another important factor is that our patients at the beginning of our studies were more selected than those in the other studies since twelve of them were referred to us because they had a history of aspirin hypersensitivity and recurrent urticaria without improvement after withdrawal of aspirin. From the high frequency of reactions to aspirin, it seems obvious that patients with urticaria should avoid this drug even if they do not have a history of worsening after aspirin.

Our earlier findings that cross-reactions between azo dyes and benzoates were common has been verified (Michaëlsson & Juhlin, 1973). Samter & Beers (1967) and Settipane & Pudupakkam (1975) reported a cross-reactivity rate to tartrazine of 8 and 15% respectively in aspirin-hypersensitive patients with symptoms of mainly asthma and rhinitis. Details of the test method were given by Settipane & Pudupakkam, who used a test dose of 0·44 mg of tartrazine and judged the reaction within 2 h. Most of our patients reacted later and to higher doses, which might explain why cross-reactivity was more common in our patients. From the present investigation, however, it is also evident that hypersensitivity to dyes or benzoates without any reaction to aspirin is not uncommon and occurred in sixteen of the seventy-five patients. A history of hypersensitivity to dyes and benzoates was obtained in 21% of the patients with positive provocations to these compounds. That the figure is lower than that for aspirin is not surprising as the additives are more or less hidden in a number of drugs and food products, whereby their intake may easily be overlooked.

The judgement of whether a reaction is positive or negative is not always easy and, in many cases, repeated provocations with placebo and additives are necessary. If the patients are in an acute stage with urticaria every day, it is impossible to continue the tests. The evaluation of the provocations must be done carefully with detailed annotations of signs and symptoms. The symptoms occur in most patients after 6–12 h but might appear as late as 20 h after provocation. Symptoms of severe facial angio-oedema mainly occurred after aspirin provocation and were more easily evaluated than a few urticarial weals.

Some patients react only with a number of subjective symptoms such as headache, tiredness, joint pains, irritability, etc. We have hitherto considered these results as probably negative although this may not be correct if repeated placebo provocations are not associated with any symptoms. For further evaluation of the relevance of such symptoms, studies of the reactions in healthy controls, as well as in patients with other skin disorders, are being undertaken.

The patients with positive provocations have been recommended a diet free from aspirin and food additives. To evaluate its effect, our results on follow-up must be compared with the expected duration of symptoms without any treatment. The total duration of urticaria of unknown aetiology has been calculated by Champion *et al.* (1969). When all cases with allergic, cholinergic and physical urticaria had been removed, they had a material of 438 cases with urticaria for at least 1 month. The prognosis was best for the patients with only urticaria and without angio-oedema. If their urticaria had lasted for 4 months, it was expected that about 23% should be free from symptoms after 12 months. The number of symptom-free patients in our study seems to follow their expectancy curves for urticaria with the exception that we have some patients with urticaria for more than 10 years who became symptom-free. Thus, many of the patients in our study who became totally symptom-free probably would have been so even without the diet. In some, there was a striking association between decrease of symptoms and start of diet. However, the group of patients from whom the effect of the diet could best be judged were those who claimed that they were much better, which means that they had only minor and occasional symptoms. After 3 months, some of them found that they had to avoid aspirin or drinks and candies that were obviously coloured. but that it was not otherwise necessary to keep to the diet. This confirms the views of Warin (1960) that many of these patients benefit by just

avoiding aspirin and is also in agreement with the findings of Warin & Smith (1975) that some patients may gradually relax their diet. Other patients found that it was necessary to be on the recommended diet. They developed weals as soon as they took something containing azo dyes or benzoates. The personal history of these patients makes it clear that it really is important for them to avoid these substances and that the diet is of great value. The results in these patients with their pronounced improvement were encouraging. Preliminary results of a similar study were recently reported by Warin & Smith (1975). They found that thirty-five of forty-five patients cleared or improved considerably and in three patients there was no effect, while five were impossible to assess. The effect of diet seems to agree well with the results presented here, but a direct comparison is difficult since they also included yeasts and penicillin in their study.

The patients were asked about the number of urticarial attacks during the month before the provocations and before the follow-up. Sixty-four per cent reported less frequent urticarial attacks at follow-up. Such information, however, says nothing about the severity, extension, and itching of the lesions. These factors are involved in the patient's subjective opinion of his urticaria and this probably explains why as many as 81% of the patients consider themselves symptom-free or much better.

As expected, there are patients who have no significant improvement despite trying to avoid aspirin, as well as dyes and benzoates. Some of them may have cross-reactions to similar naturally occurring substances or have later been found to be sensitive to other additives. For some patients other factors might be of greater importance.

To maintain the diet is fairly simple if the contents of foods and drugs are properly declared. If they are not, it is certainly more difficult. It seems reasonable that full information on products should be given in order to make a free choice possible. The need for this is becoming increasingly evident.

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