

Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics*

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Forty-five patients with moderately severe perennial bronchial asthma were challenged by ingestion of: acetylsalicylic acid (ASA); 4 azo dyes (tartrazine, sunset yellow, amaranth, and ponceau); 3 non-azo dyes (erythrosine, brilliant blue, and indigotin); sodium benzoate (NaB); parahydroxybenzoic acid (OHBA); butylated hydroxyanisole (BHA); and butylated hydroxytoluene (BHT). A fall in forced expiratory volume in one second (FEV₁) greater than 25% from baseline was considered positive. Seven patients who gave an unequivocal history of aspirin intolerance were not challenged with ASA; an additional 13 had positive open challenges to ASA, giving an apparent incidence of aspirin sensitivity of 20/45. The presence of nasal polyps, sinusitis, or the regular use of corticosteroids, either singly or in combination, was not associated with an increased incidence of reactions to ASA. Significant bronchoconstriction to open challenges with agents other than ASA was less frequent. Positive open challenges to all substances except aspirin were followed by double-blind challenges which were positive in only 3 instances: 1 each with erythrosine, ponceau, and NaB/OHBA. Our findings confirm that ASA intolerance is relatively common but suggest on the other hand that reactions to dyes and preservatives are an uncommon cause of clinically significant bronchoconstriction in moderately severe perennial asthmatics.

That the ingestion of small amounts of acetylsalicylic acid (ASA) can precipitate severe and sometimes life-threatening bronchoconstriction has long been appreciated and is well documented in the medical literature.¹⁻⁴ More recently, a number of ubiquitous food and drug additives, primarily used as colorants and preservatives, have also been incriminated in the production of bronchoconstriction, particularly

in individuals who react in a similar manner to aspirin.⁵⁻⁹

This study was designed to determine the incidence of dye- and preservative-induced bronchoconstriction in a population with moderately severe bronchial asthma. We studied perennial, nonallergic, or "intrinsic" asthmatics since in many series a higher incidence of ASA intolerance has been reported in this group than in allergic or "extrinsic" asthmatics.¹⁰⁻¹⁴ Most previous reports have shown a strong association between ASA sensitivity and similar reactions to dyes and preservatives.^{5-8, 15} There are, however, also reports of patients with such sensitivities in the absence of ASA intolerance.^{16, 17}

MATERIALS AND METHODS

Patient selection

Forty-five patients with perennial asthma volunteered to take part in this study. Patients were selected from asthmatics treated by the Allergy-Immunology Service of Fitzsimons Army Medical Center on the basis of perennial

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wheezing of moderate severity requiring maintenance use of bronchodilators, particularly if the history suggested precipitation of wheezing by aspirin or food containing large amounts of coloring agents or preservatives. Sixteen of the subjects were males ranging in age from 17 to 62; 9 were on prednisone ranging from 5 mg every other day to 40 mg every day; 2 of these were also using inhaled beclomethasone. Twenty-nine of the subjects were female, ranging from 15 to 62 years of age; 15 were on prednisone, 7.5 mg every other day to 60 mg every day; 3 were also on inhaled beclomethasone, and another was on beclomethasone alone. Duration of asthma varied from 2 to 40 years. Nasal polyposis was documented in 8 of 16 males and 14 of 29 females. Rhinitis was present in 9 of 16 males and 18 of 29 females. All 45 subjects were on maintenance methylxanthine bronchodilators; 26 were also taking adrenergic agonists.

Challenge schedules

The patients first underwent open challenge over several days and in variable order with the following drugs and additives: (1) ASA; (2) tartrazine (FD&C yellow No. 5); (3) three azo dye mix consisting of amaranth (FD&C red No. 2), ponceau (FD&C red No. 4), and sunset yellow (FD&C yellow No. 6); (4) three non-azo dye mix consisting of brilliant blue (FD&C blue No. 1), erythrosine (FD&C red No. 3), and indigotin (FD&C blue No. 2); (5) sodium benzoate (NaB) and parahydroxybenzoic acid (OHBA); (6) butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

ASA, sodium benzoate, OHBA, BHA, and BHT were administered as white powders in clear gelatin capsules and could not be visually differentiated. The dyes were reconstituted from powdered form in distilled water; appropriate doses were then administered in additive-free grape juice concentrate. Although the patients could tell whether they were receiving a liquid (dye) or a powder (preservative or ASA), the test doses were not further identified, making the open challenges effectively single-blind. Patients who thought they might be ASA-intolerant did not know which of the capsules contained ASA.

With the exception of ASA, all positive open challenges were repeated under double-blind conditions at a later date, usually 2 weeks to 1 month later. In the double-blind challenges, all agents were administered separately, not in mixes as in the open tests, and only one agent was given each day. An equal number of days of placebo challenges with grape juice concentrate or lactose-filled gelatin capsules were employed in the double-blind challenges. If more than one dose per day of dye or preservative was given, then the same number of doses were given on placebo days. Doses used for the double-blind challenges were equal to or greater than those which produced the positive challenge in the open testing. Whenever feasible, positive double-blind challenges were repeated—on some occasions, three and four times.

Schedules used for the challenges are given in Table I. At the onset of the study, lower doses of some of the agents

TABLE I. Challenge schedule

Agent	Sequential doses*
ASA†	75, 150, 375 mg
BHA/BHT	125, 250 mg each
NaB/OHBA	50, 100, 250 mg each
	125, 250 mg each
Tartrazine	2.5, 5, 10 mg
	5, 20 mg
Azo dyes (Mix No. 1)	2, 4, 10 mg each
Amaranth	5, 20 mg each
Ponceau	
Sunset yellow	
Non-azo dyes (Mix No. 2)	5, 10 mg each
Brilliant blue	5, 20 mg each
Erythrosine	
Indigotin	

ASA, BHA, BHT unchanged. (See text for abbreviations.)

*First line is dosage for first 13 subjects; second line is dosage for remainder of subjects.

†Patients with an unequivocal history of reaction to aspirin were not challenged. Those with equivocal histories received smaller initial doses of aspirin.

were used for testing as indicated by the first line for each agent in Table I. After the first 13 patients, the doses were increased as shown in the second dosage lines. The dosage schedules for ASA, BHA, and BHT were not changed. The order in which the agents were administered was varied from patient to patient. Patients were instructed to avoid foods with artificial coloring or preservatives for 1 to 2 days prior to the challenge.

Initially, the patients' routine bronchodilator medication was withheld following the bedtime dose. This practice, however, was attended by a number of false-positive tests as airway irritability increased due to waning drug effect. Therefore, after the first 12 subjects, patients were instructed to take their morning medication in the routine manner, usually 1 to 2 hr before reporting to the clinic. Testing was usually completed, therefore, within 4 to 5 hr of ingestion of bronchodilator medication.

Pulmonary function testing

Forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), and peak expiratory flow rate (PEFR) were measured using a Jones Pulmonary Datamatic (Jones Equipment Company, Oakbrook, Ill.). Three determinations were made at 5-min intervals prior to the challenge to ensure a stable baseline; if the values were widely divergent or showed a downward trend, the patient was not challenged that day. A decrease of 25% from baseline FEV₁ was considered a positive challenge. Pulmonary function testing was repeated at 20-min intervals following ingestion of the test dose. If no significant change in FEV₁ occurred by 1 hour, the next larger dose was given. A positive challenge terminated testing for that day.

TABLE II. Challenge results

Agent (maximum dose)	Open		Double-blind	
	No. tested	No. positive	No. open-positive tested	No. positive
ASA (450 mg)	38	13	—	—
Tartrazine (20 mg)	44	7	7	0
Azo dyes (20 mg)	43	4	4	1
Non-azo dyes (20 mg)	42	3	2	1
NaB/OHBA (250 mg)	43	2	2	1
BHA/BHT (250 mg)	43	0	—	—

See text for details and abbreviations.

TABLE III. Clinical features of responders and nonresponders

Sex	Responder*	Nonresponder
Male	7	9
Female	17	12
Age	40.4	39.5
Duration of asthma	10.5	15.3
Steroid usage	10	10
Nasal polyposis	13	9
Sinusitis	10	5
Rhinitis	16	11

*Includes 20 ASA-sensitive, 3 who responded to double-blind challenge with dyes and preservatives, and 1 positive to the non-azo dye mix on open challenge and not double-blind challenge.

RESULTS

The results of the open and double-blind challenges are summarized in Table II. ASA challenges were positive, resulting in a fall of 25% or greater in FEV₁ in 13 of 38 subjects tested. Doses which produced the positive challenges ranged from 30 mg (small dose used because of a suspicious history) to 450 mg (patient negative at 150 mg). Four subjects responded to doses of 75 mg, 2 to a dose of 150 mg, 4 to 375 mg, and 2 to 450 mg. Seven additional patients had strong unequivocal histories, that ASA, and often other nonsteroidal anti-inflammatory agents, had repeatedly caused bronchoconstriction and were therefore not challenged to ASA. Another patient developed acute urticaria following 375 mg of ASA, but her FEV₁ did not decline 25% from baseline. The incidence of ASA-induced bronchoconstriction in these selected patients thus was possibly as high as 44%, and total adverse reactions, 47%. None of the positive open ASA challenges was repeated double-blind.

Bronchoconstriction following challenge with dyes and preservatives was uncommon. Seven of the 44 patients tested with tartrazine had a significant fall in pulmonary function on open challenge; however, in

none of these 7 was the positive response to tartrazine confirmed on double-blind testing.

Of 43 tested to the azo dyes (Mix No. 1), 4 were positive on open challenge. All four were retested double-blind to the individual dyes and in only 1 patient was there a positive test. This patient underwent double-blind challenge with ponceau twice and reacted on both occasions. With the non-azo dyes (Mix No. 2), 3 of 42 patients were positive on open challenge. Only 2 were retested double-blind; of these, 1 was negative to all 3 dyes while the other was positive to erythrosine. This patient had 3 positive double-blind challenges to erythrosine over a period of 7 weeks. Two years later, the double-blind challenge was repeated once more, and this time it was negative.

Open challenges with the combination of sodium benzoate and *p*-hydroxybenzoic acid were positive in 2 of 43 patients. When double-blinded, only 1 proved positive. This patient was sensitive to both NaB and OHBA. Two years later, the double-blind challenges to NaB, OHBA, and placebo were repeated, and this time the patient did not react. There were no positive open challenges to the combination of BHA or BHT in 43 subjects tested.

There was no overlap between the ASA-intolerant group and those who reacted to the dyes and benzoates. None of the 3 who responded to double-blind challenges with ponceau, erythrosine, or the benzoates, nor the additional responder to the non-azo dye mix in open challenge who did not undergo double-blind challenge, had a positive ASA challenge or an unequivocal history of ASA intolerance.

Responders and nonresponders to ASA, dyes, and preservatives were compared (Table III). Complete information was available on 44 of the 45 subjects. The Fisher test showed no statistically significant differences between responders and nonresponders for mean age, mean duration of asthma, sex, presence of nasal polyposis, sinusitis, or rhinitis. Steroid usage was evaluated in terms of low, moderate, and high

doses, and there were no statistically significant differences between responders and nonresponders in any category of steroid dose. This lack of discriminating clinical parameters was true whether ASA responders were considered separately or in combination with the dye and preservative responders.

One patient merits further description. This subject had positive open challenges to all the dyes, but a varying pattern of positive reactions to dyes and placebos on double-blind testing. After extensive repeat testing, it became apparent that when he did not take his maintenance bronchodilator medication on the morning of testing, he had positive tests; and when the medication was taken, the tests were negative. These false positive tests were thought to be due to waning bronchodilator effect perhaps aggravated by the effort of repeated forced expiratory maneuvers.

DISCUSSION

In 1967, Chafee and Settippane⁵ reported asthmatic symptoms precipitated by tartrazine, FD&C red dye No. 4 (both azo dyes), and sodium benzoate in an aspirin-sensitive asthmatic woman. In 1973, Rosenthal and Zetterstrom⁸ reported positive challenges with ASA, NaB, OHBA, and a number of dyes used to color foods and medicines. Also in 1973, Fisherman and Cohen⁹ reported that a group of patients with asthma and rhinitis were sensitive to the antioxidants BHA and BHT.

In this study of 45 patients with bronchial asthma, the incidence of bronchoconstriction following aspirin ingestion was 44%. While the positive response to tartrazine on open challenge (single-blind) was 16%, none proved positive on double-blind testing. Double-blind challenge with the other azo dyes resulted in only one positive test with ponceau for an incidence of 2%. With the non-azo dyes there was a similar rate of positive reactions of 2% with one positive double-blind test to erythrosine (if one includes the patient not double-blinded, the possible incidence would rise to 5%). NaB and OHBA were each positive on double-blind challenge only once and these were in the same patient, again giving an incidence of 2%. There were no positive challenges with either BHA or BHT.

The incidence of adverse reaction to ASA in the present study is higher than any reported in the literature. This should not be taken as a true incidence of aspirin sensitivity in the general population of asthmatics, but rather as a reflection of our effort to select a high-risk population to study. Also, since it was not the purpose to study aspirin intolerance, we chose not to employ double-blind confirmation of apparent adverse reactions to aspirin. Thus, the true incidence of

aspirin sensitivity in this group may have been less than the suggested 44%.

Considering the high incidence of ASA sensitivity in the group studied, the incidence of bronchoconstriction following ingestion of benzoates and dyes is much lower than would be expected from some reports in the literature; however, the reported incidence varies widely with differing criteria employed for a positive test and whether the study was conducted under double-blind conditions. Samter and Beers reported an incidence of bronchoconstriction with tartrazine of 6% in 222 ASA-sensitive patients, but none in 40 non-ASA-sensitive asthmatics.⁶ Settippane and Pudupakkam¹⁵ reported that tartrazine produced a fall in FEV₁ of greater than 20% plus clinical signs of bronchoconstriction in 9% of 34 patients who had developed asthma with aspirin ingestion.¹⁵ Vedanthan and co-workers¹⁸ found no instance of tartrazine sensitivity in 54 asthmatic children 10 to 17 yr of age, but only 3 of their patients had had a significant fall in pulmonary function following ASA challenge.¹⁸ Delaney,¹⁹ on the other hand, encountered only two mild responses to tartrazine (falls in FEV₁ of 9% and 17%) in 35 aspirin-sensitive asthmatics.

A higher incidence of tartrazine sensitivity has been reported in two studies from Scandinavia. Stenius and Lemola¹⁶ reported on adverse reactions to tartrazine in 114 hospitalized patients. Fifty percent of ASA-sensitive and 20% of non-ASA-sensitive asthmatics met their criteria for a positive reaction, which was a 20% fall in peak flow rate. Rosenthal,¹⁷ employing either the same 20% fall in PEF, the development of pronounced new symptoms, or the repeated documentation of lesser reactions as criteria for a positive test, reported an incidence of tartrazine sensitivity in 592 asthmatic patients of 17% in those sensitive to ASA and of 1% in those not ASA-sensitive. The same author, studying the response to sodium benzoate in 531 asthmatic patients, reported positive reactions in 14% of ASA-sensitive and in 1% of non-ASA-sensitive patients. It should be noted, however, that in the studies by Stenius and Lemola and by Rosenthal there were no true placebo challenges; a single placebo dose at the beginning of the test session was invariably followed by active drug. Thus, any fall in pulmonary function due to waning effect of bronchodilators or reflex bronchoconstriction due to the effort of repeated forced expiratory maneuvers would be interpreted in these studies as a drug effect.

Several factors could account for a lower incidence of positive reactions in our study. Dose does not appear to be a factor, since the doses of tartrazine and benzoic acid preservatives we employed were as high as in any of the previously cited studies, and consid-

erably higher than in some.¹⁵ Another major factor causing differing rates of reactions is the criteria for a positive reaction. The FEV₁ is less variable than the peak flow,^{18, 20} and thus changes in FEV₁ of 20%¹⁵ or 25% as in our study represent much more significant variations than the 20% change in peak flow employed in some other studies.^{16, 17} It has been reported that a refractory period of up to 3 days may follow a positive aspirin challenge.²¹ Although a similar refractory period has not been reported with reactions to dyes and preservatives, it remains a likely possibility. Therefore, our patients were in most instances instructed to avoid dyes and preservatives for 1 to 2 days prior to challenge, and positive open challenges were not repeated under double-blind control until 2 to 4 weeks later.

Another possible cause for variations in challenge results is that the reaction to dyes or preservatives might be masked by medication. It has been reported that cromolyn sodium can block the bronchoconstrictor response to ASA in some patients.^{22, 23} None of our patients was on cromolyn. It has been suggested but not proved that prednisone in doses greater than 15 mg per day may block the reaction to aspirin, dyes, and preservatives.¹⁷ If indeed prostaglandins are involved in these adverse reactions, the ability of corticosteroids to block the generation of arachidonic acid, the precursor of prostaglandins, would provide an explanation for steroid inhibition of the adverse response to ASA. However, statistical analysis of our data showed no difference in the rate of adverse reactions between patients on large doses of steroids and those on low doses or no steroids.

A major difference among the studies cited is the handling of methylxanthine and beta adrenergic bronchodilator therapy the day of the challenge. In some studies, these medications were omitted for 6 to 8 hr prior to challenge.^{16, 17} In another study, a routine dose of theophylline was administered with the test drug.¹⁸ In our study, we initially withheld bronchodilators following the evening dose. We found this practice resulted in several positive challenges with both test substances and placebos. Therefore, in the latter part of the study, we routinely administered all of the patients' bronchodilator medication at the customary time. Challenges were begun 1 or 2 hr later. Although it is possible that this routine administration of bronchodilators could have masked a minor degree of reactivity, we felt that repeated positive responses to placebo challenges would make the results of the study uninterpretable. Bronchial lability due to withholding medication may have contributed to some of the high rates of dye and preservative sensitivity that have been reported.^{16, 17} Indeed,

we suspect that some of our positive open challenges may have reflected this same waning of medication. With our double-blind challenges, on the other hand, usually only one dose was employed, so that the testing was generally completed by 3 to 4 hr following the morning bronchodilators.

An interesting observation was that 2 of our patients who had repeatedly positive double-blind studies when initially tested were negative to these same agents when rechallenged 2 yr later. Other investigators have reported loss of known sensitivity to ASA¹⁷ and have suggested that sensitivity to aspirin, dyes, and preservatives may vary with severity of the underlying asthma.^{7, 17, 24}

Finally, we include a comment on the demographic data on our ASA responder and nonresponder patients. There was no difference between those sensitive to ASA, dyes, and preservatives and those without sensitivity in regard to any parameter, including requirement for chronic corticosteroid medication, incidence of nasal polyps, and sinusitis. This lack of close correlation has been reported before.^{18, 25} We feel nasal polyps and sinusitis, requirement for corticosteroids, and ASA intolerance are each associated with severe asthma and therefore are epiphenomena not necessarily causally related to each other. "Triad asthma" is an attractive but misleading term to describe those patients intolerant of ASA, many nonsteroidal anti-inflammatory drugs, and occasionally dyes and preservatives.

In summary, this study, employing strict double-blind challenges to confirm positive open challenges, suggests that clinically important intolerance to dyes and preservatives is uncommon in patients with moderately severe perennial bronchial asthma. ASA intolerance, in the same group, was quite common. No patients in the study demonstrated a bronchoconstrictor reaction to BHA or BHT.

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