

Tartrazine and benzoate challenge and dietary avoidance in chronic asthma

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Summary

This study undertook to determine the usefulness of tartrazine and benzoate challenge and dietary avoidance in the management of patients with chronic asthma. Double-blind ingestion-challenge tests were performed on separate days with lactose, tartrazine, benzoate and acetylsalicylic acid (ASA). Of the twenty-eight subjects challenged, one responded to tartrazine and one to benzoate. Two additional subjects responded to ASA and a further eight were not tested with this material because of a definite history of sensitivity. Twenty-four subjects completed 1 month periods of observation while first on a normal diet and then while on a tartrazine-benzoate avoidance diet. No improvement occurred during the modified diet in anyone with positive challenge-tests or in all, but one, of those with a history of ASA idiosyncrasy; paradoxically, several of these subjects worsened during this period. We conclude that tartrazine-benzoate dietary avoidance was not of value in the management of the chronic asthmatic in this study, even among patients who respond to challenge with these substances or have ASA idiosyncrasy.

Introduction

Idiosyncrasy to acetylsalicylic acid (ASA) has been reported in 2.0%–44% (Falliers, 1973; Weber *et al.*, 1979) of asthmatics, and a proportion of the same patients have been found to react in a similar manner to food colourings and preservatives (Weber *et al.*, 1979; Samter & Beers, 1967; Settupane & Pudupakkam, 1975; Stenius & Lemola, 1976; Vedanthan *et al.*, 1977; Delaney, 1976; Chafee & Settupane, 1967; Rosenthal, 1977; Spector, Wangaard & Farr, 1979; Juhlin, Michaelsson & Zetterstrom, 1972; Rosenthal & Zetterstrom, 1973). Many reported challenge-studies have employed an open design, (Weber *et al.*, 1979; Stenius & Lemola, 1976; Rosenthal, 1977) but the frequency of positive results has been found to be appreciably reduced when a

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double-blind procedure is followed (Weber *et al.*, 1979; Samter & Beers, 1967; Vedanthan *et al.*, 1977; Delaney, 1976; Spector *et al.*, 1979).

Asthmatics having chronic symptoms and/or a history of ASA idiosyncrasy are sometimes treated empirically with a tartrazine-benzoate avoidance diet, but the value of this approach has never been studied directly. The purpose of the present study was to determine the frequency of a positive response to ingestion challenge with tartrazine and benzoate, performed using a double-blind design, in a group of chronic asthmatics and to assess the clinical usefulness of the avoidance of both materials in the absence of exposure to non-steroidal anti-inflammatory agents.

Materials and methods

Patients were assessed by means of a detailed history, physical examination, skin-testing with allergen extracts and maximal expiratory flow-volume curves before and after an inhaled bronchodilator. They were then challenged orally on separate days with placebo, tartrazine, benzoate and, in some patients, ASA. Subsequently, each subject was assessed during 1 month when allowed a normal diet, followed by a second month in which tartrazine, benzoate and non-steroidal anti-inflammatory agents were avoided.

Patients

Twenty-eight ambulatory asthmatic patients were chosen from several private practices and from the Asthma Clinic of The Gage Research Institute. The only selection criteria were the ability of the patients to understand the requirements of the study, their availability to attend the clinic for the necessary number of visits and the presence of sufficiently severe asthma to motivate them to complete the full protocol. The study was explained in detail to all subjects following a procedure approved by a committee of the Office of Research Administration of the University of Toronto and a written consent was obtained in all instances.

Skin-testing

Skin-tests were performed using the following group of nine common inhalant-allergens (Hollister Stier Laboratories, Canada):

House-dust mixture (prick test 1:10 weight/vol. or intradermal 1000 protein nitrogen units (PNU/ml), *Dermatophagoides farinae* (1:50 or 1:2000), tree-pollen mix (1:20 or 500), grass-pollen mix (1:20 or 500), ragweed mix (1:20 or 500), *Hormodendrum* (1:10 or 1000), *Alternaria tenuis* (1:10 or 1000), *Aspergillus* mix (1:10 or 1000), feather mix (1:10 or 1000) and control solution.

A mean weal diameter of 2 mm or greater on prick testing and a 10 mm or greater weal diameter with surrounding erythema on intradermal-testing was regarded as a positive reaction after any response to the diluent had been subtracted.

Challenge procedure

Subjects were challenged with lactose, benzoate, tartrazine and ASA in random order, double-blind, on separate days under the supervision of a physician. Those with a clear history of ASA-induced asthma did not receive the challenge with ASA. Subjects were asked to adhere to a tartrazine and benzoate-free diet for 24 hr before each challenge-test. The patients continued their usual medications prior to the challenge test on each day, since the participants in this study would otherwise have been likely to

become symptomatic. However, all challenges of a given subject were started at the same time of day. Each material, including lactose, was given first in a small dose and then in a larger dose 2 hr later, if no response had occurred. Tartrazine was utilized in doses of 1.5 and 15 mg, sodium benzoate at 25 and 250 mg and ASA at 30 and 300 mg in the absence of a history of ASA-induced asthma. The maximum dose of tartrazine was chosen on the basis of being equivalent to the daily average for a North American diet. Subjects with an equivocal history of ASA-induced symptoms were given ASA at 15 and 50 mg on one day and then at 150 and 300 mg on a different day. Each dose was prepared in an identical-sized clear-gelatin capsule which was handed to the patient in a coded envelope and subsequently not seen by the investigators or technical staff. Subjects were asked to close their eyes while taking the capsules as the colour of tartrazine could not otherwise be completely hidden.

Maximal expiratory flow-volume curves were performed on each test day, prior to challenge, 2 hr after each challenge dose, and at any time the patient developed respiratory symptoms. This procedure was carried out using a wedge spirometer equipped with a 1 sec time-marker; replicate curves for a given subject were superimposed, and the manoeuvre was repeated until two tracings were obtained that corresponded within 5.0% both for forced vital capacity (FVC) and for flow over the lowest 70% of vital capacity. The best of the two superimposable flow-volume curves was used to measure FVC, forced expiratory volume in 1 sec (FEV_1), maximal expiratory flow at 50% of vital capacity ($\dot{V}_{max_{50}}$) and $\dot{V}_{max_{25}}$. Challenge tests were deferred if the baseline measurements revealed the FEV_1 to be less than 1.0 litre. A 20% fall in FEV_1 , compared with the baseline reading for that day, was considered a positive challenge. In the event of a positive challenge, no further test capsules were given for that day and pulmonary-function tests were repeated at intervals until the values returned towards the baseline. Bronchodilator therapy was administered as necessary following a positive response. Challenge tests with the different materials were conducted at intervals of 1 day or longer; the interval was increased to a minimum of 5 days following any clinically-positive response.

In addition, peak-flow measurements were made in triplicate using a Wright peak-flow meter immediately following the completion of the challenge procedure, at intervals of 4 hr whenever the subjects were awake and at the time of any worsening of respiratory symptoms during the 24 hr following each challenge. The highest of each group of three peak-flow measurements was recorded by the subject on a diary sheet. The occurrence of any upper or lower respiratory-symptoms during the day of the challenge test were recorded.

Dietary observations

All subjects were asked to participate in a 2-month period of dietary assessment. Neither patient nor physician were aware of the challenge results until the end of this period. During the first-month symptoms, medications and four-times daily peak-flow measurements were recorded on diary sheets each morning and evening while subjects ingested their usual diet and medications. An asthma-day score was rated between 0–5, depending on the duration of wheezing (a scale of 1 indicating wheezing for less than 1 hr and 5 indicating wheezing all day), and a night score rated 0–5, depending on the number of times the patient was woken by wheezing (a score of 5 indicating the subject was awake all night). The numbers of tablets, capsules or inhalations of medications were recorded daily. During the second month similar records were made while on a

diet avoiding commercially added tartrazine and benzoate and eliminating ASA and other non-steroidal analgesics (dietary instructions are available on request). Patients were seen by a physician at the onset of the dietary period and at the conclusion of each of the monthly intervals, at which times nasal symptoms and their frequency were recorded as well as the level of exercise capacity, and physical examination of the nose and chest was performed. A maximal expiratory-flow volume curve was recorded at each visit.

Statistical methods

Statistical analyses were made using Student's paired t-test and the chi-square test.

Results

Twenty-eight adult asthmatics took part in this study, all of whom required daily medication for control of their symptoms, including 82% who took oral and/or inhaled corticosteroid therapy (Table 1). Each patient had a history consistent with episodic airways-obstruction, diffuse expiratory-rhonchi heard on auscultation of the chest and reversibility of at least 15% in the FEV₁, the $\dot{V}_{max50}$ or the $\dot{V}_{max25}$ after inhalation of a bronchodilator aerosol. All were middle class and only one, a Chinese man, was not Caucasian. The challenge tests were completed by all twenty-eight subjects and the dietary assessment by twenty-four.

The average of the results of the pulmonary-function tests for all subjects showed no significant changes following ingestion of any of the challenge substances (Table 2). Nevertheless the results of the individual subjects demonstrated one positive response to each of benzoate and tartrazine and two to ASA, all in separate subjects (Table 3). The benzoate-positive subject and one ASA responder also developed worsening of nasal symptoms during the challenge. There were no positive responses to lactose. Also, none of the subjects showed a response to challenge which was delayed in onset beyond 2 hr after ingestion of the second test-dose.

Twenty-four of the twenty-eight challenged patients completed the dietary

Table 1. Characteristics of asthmatic patients

	Patients completing challenge tests	Patients also completing dietary assessment
<i>n</i>	28	24
Age (years)	52 ± 14*	53 ± 12
Male: Female	14: 14	13: 11
Duration of asthma (years)	15 ± 14	14 ± 15
Medication requirements (%)		
Oral or inhaled bronchodilators	93	96
Oral or inhaled corticosteroids	82	64
Inhaled cromoglycate	7	4
Nasal symptoms (%)	75	75
Nasal polyps/polypectomy (%)	43	42
ASA idiosyncrasy on history (%)	28	21
Positive allergy skin tests (%)	39	37

*Mean ± s.d.

Table 2. Mean FEV₁ results prior to challenge and 2 hr after each challenge dose

Challenge	<i>n</i>	FEV ₁ (litres)		
		0	Dose 1	Dose 2
Lactose	28	2.2 ± 0.9*	2.1 ± 0.8	2.1 ± 0.8
Benzoate	28	2.2 ± 0.9	2.1 ± 0.9	2.1 ± 0.9
Tartrazine	28	2.1 ± 0.9	2.0 ± 0.9	2.0 ± 0.8
ASA	20	1.9 ± 0.7	1.9 ± 0.8	1.9 ± 0.7

*Mean ± s.d.

assessment without knowledge of the challenge-test results. These included all four challenge-positive subjects and seven out of eight ASA-history positive subjects. The average of the diary variables for the entire group, including the peak-flow measurements, showed no improvement during the period of the avoidance compared with the normal diet (Table 4).

Each diary variable was examined to assess the number of individual subjects who underwent a significant improvement or worsening during the period of the avoidance diet, compared with the normal diet (Table 5). This was done using Student's paired *t*-tests to compare the results of the dietary periods for each subject and variable. Four subjects needed significantly greater doses of oral corticosteroids during the avoidance diet and four required less. Five subjects had a significant worsening of peak-flow rates while only two improved. Symptoms during the day and other medication requirements were improved during the avoidance diet in more subjects than during the normal diet, but some of these differences were attributable to increased oral-corticosteroid usage. Although a significant change was expressed as that associated with

Table 3. Positive challenge-results following tartrazine, benzoate and ASA ingestion in twenty-eight subjects

Subject No.	Challenge	Dosage	FEV ₁ change(%)*	
			Dose 1	Dose 2
539	lactose		-3.3	-6.1
	tartrazine	1.5 and 15 mg	-5.9	-20.4
625	lactose		-2.0	0.0
	benzoate	25 mg	-29.0	not given
352	lactose		-9.2	-9.2
	ASA	15 and 50 mg	-6.4	-28.2
597	lactose		-13.5	-6.7
	ASA	30 and 300 mg	-2.8	-21.4

*Changes in FEV₁ are expressed as a percentage from the initial pre-challenge baseline recorded for that day. A negative value indicates a fall in FEV₁. For each patient the baseline FEV₁ did not vary more than 10% on each challenge day.

Table 4. Mean daily diary results of twenty-four subjects

Entries	Normal diet	Avoidance diet
Asthma-day score	1.8 ± 1.3*	1.8 ± 1.3
Asthma-night score	1.2 ± 0.7	1.2 ± 0.7
Inhaled bronchodilator (no. puffs/day)	3.6 ± 3.2	3.4 ± 3.4
Oral bronchodilator (no. tabs/day)	2.4 ± 2.3	2.4 ± 2.2
Inhaled corticosteroid (no. puffs/day)	5.7 ± 3.3	5.0 ± 3.5
Oral corticosteroid (no. tabs/day)	1.0 ± 1.4	1.1 ± 1.5
Peak flow (l/min)	281 ± 114	278 ± 112

*Mean ± standard deviation

$P \leq 0.05$, the proportion of subjects improving *vs* those worsening for each diary variable was not materially changed by reducing the significance level to $P = 0.007$, to correct for the number of variables examined.

We similarly examined all of the diary variables for each subject by Student's paired *t*-test to determine whether there was significant overall improvement, worsening or no change during the elimination as compared with the normal diet (Table 6). Taking $P \leq 0.05$ as significant, there was overall improvement in eight subjects, three of whom were able to reduce their oral or inhaled corticosteroids without worsening of other diary variables during the elimination diet, and five who had significant improvement in other diary variables without worsening in others. Only one of these eight subjects

Table 5. Number of subjects showing significant change on avoidance diet compared with normal diet

	Status on avoidance diet	
	better*	worse
Asthma-day score	7 (1)†	3 (1)
Asthma-night score	1 (1)	3 (2)
Inhaled adrenergic	6 (1)	3
Oral bronchodilator	3 (1)	1
Inhaled corticosteroid	6 (2)	2
Oral corticosteroid	4	4
Peak flow	2 (1)	5

*Subjects were classified as being better or worse if a given variable showed a change associated with $P \leq 0.05$ between the two dietary intervals.

†The number in brackets indicates those subjects who improved or worsened for a given variable and also significantly increased their usage of oral corticosteroid.

Table 6. Changes in diary variables expressed as *P* values of Student's paired *t*-tests of individual subjects while on the modified diet, compared with the normal diet

Patient No.	Asthma-day score (<i>P</i>)	Asthma-night score (<i>P</i>)	Inhaled bronchodilator (<i>P</i>)	Oral bronchodilator (<i>P</i>)	Inhaled steroid (<i>P</i>)	Oral steroid (<i>P</i>)	Peak flow (<i>P</i>)	Overall change or modified diet* (<i>P</i>)
120			+ < 0.01†	- < 0.001*			- < 0.001†	+/-
125						+ < 0.005†	- < 0.001	+/-
183					+ < 0.001†	+ < 0.001		+
188							+ < 0.005	+
201‡			- < 0.001				- < 0.001	-
214‡								0
269							- < 0.0010	-
294			+ < 0.025	+ < 0.0010				+
317‡								0
352‡	- < 0.05†							-
385‡	+ < 0.005				+ < 0.001	+ < 0.001		+
391	+ < 0.05		+ < 0.001			+ < 0.025		+
441	+ < 0.025				- < 0.001			+
482	+ < 0.02							-
494	+ < 0.001							+
536		+ < 0.02			+ < 0.001	- < 0.05		-
539‡			- < 0.005				- < 0.05	-
542	+ < 0.01		+ < 0.05	+ < 0.02				+
547‡	+ < 0.05	- < 0.02	+ < 0.01	+ < 0.001		- < 0.001		-
553				- < 0.02				-
554‡	- < 0.001	- < 0.001			+ < 0.001	- < 0.001	+ < 0.005	-
576‡					- < 0.001			-
597‡						- < 0.02		-
625‡	- < 0.01	- < 0.02	+ < 0.02		+ < 0.001			+/-

*Overall change for a given subject is expressed as + if improved on the modified diet, - if worse, +/- if ambiguous and 0 if unchanged. A significant increase in oral corticosteroid intake or significant deterioration of any variables without improvement in others is taken as overall worsening.

†+ = improved - = worse, while on the modified diet.

‡Subjects positive by history or challenge to ASA or by challenge to tartrazine or benzoate

who improved with the elimination diet had a history of ASA idiosyncrasy and none had positive challenge-tests. Conversely, eleven subjects worsened overall on the elimination diet, six requiring increased doses of oral or inhaled corticosteroids and five worsening in other diary variables; of these, four had a history of ASA idiosyncrasy, two were challenge-responsive to ASA and one responded to tartrazine. The remaining five subjects showed no overall change or exhibited ambiguous changes during the dietary assessments; these included two ASA-sensitive subjects by history and the one who responded to benzoate challenge. If we reduced the cut-off for P value to $P=0.007$ to adjust for the number of variables examined, eight subjects improved overall, eight worsened and eight remained unchanged or showed ambiguous changes. The benzoate-challenge positive subject thereby improved as did one ASA-history positive subject. The tartrazine-challenge positive subject and four ASA-history positive subjects worsened while two ASA-history and two ASA-challenge positive subjects were unchanged.

Nasal symptoms nevertheless did improve subjectively in six patients during the elimination diet, including the benzoate-challenge positive subject and three of those having a history of ASA idiosyncrasy. Rhinitis did not worsen in any subject during the elimination diet nor improve in any on the normal diet. Of the six patients whose nasal symptoms improved on the elimination diet, three also showed coincident, significant improvement in their asthma, one an ambiguous change, one no change and one a worsening of asthma.

There was a history of respiratory infection in four subjects during the period of the normal diet and in two subjects while on the elimination diet. In addition, during the elimination diet one subject described increased emotional-stress, another increased smoke-exposure and in a third the diet coincided with the ragweed-pollen season which usually resulted in a worsening of symptoms.

Discussion

The 4% frequency of tartrazine idiosyncrasy found in our study is comparable to that of the 0.0–7.0% reported in other studies performed utilizing a double-blind design (Weber *et al.*, 1979; Samter & Beers, 1967; Vedanthan *et al.*, 1977; Delaney, 1976; Spector *et al.*, 1979). Nevertheless, there were other differences in technique among all of these studies, such as the dosage of tartrazine, the profile of the subjects studied and whether or not medication was withheld prior to challenge. Thus, either these results may not be valid for comparative study or these variables may not have an impact on the outcome. On the other hand, the use of a double-blind design clearly appears to be important, since the frequency of positive results was found to be 16–28% in those studies where this was not done (Weber *et al.*, 1979; Juhlin *et al.*, 1972). Consistent with this interpretation Weber and co-workers reported a 16% frequency of responses to tartrazine following challenge with an open design, which reduced to 0.0% when the same subjects were challenged utilizing a double-blind technique.

There have been few reports on the frequency of benzoate-challenge responses in asthmatics (Weber *et al.*, 1979; Rosenthal, 1977; Rosenthal & Zetterstrom, 1973). However, the available results, obtained utilizing a double-blind design, are consistent with those of our study (Weber *et al.*, 1979).

Previous studies have reported that the bronchoconstrictor idiosyncratic response to tartrazine occurs primarily among asthmatics who show a similar sensitivity to ASA

(Samter & Beers, 1967; Settupane & Pudupakkam, 1975; Stenius & Lemola, 1976; Rosenthal, 1977; Spector *et al.*, 1979). The concurrence of the dual idiosyncrasy has been variably found in 8.0–44% of aspirin-sensitive asthmatics. Nevertheless, idiosyncrasy to azo dyes and benzoate has been described in subjects who do not have idiosyncratic responses to ASA (Weber *et al.*, 1979). Our findings of only one positive challenge-response to tartrazine and one to benzoate do not allow us to draw conclusions about the relative frequency among ASA-idiosyncratic and ASA-tolerant subjects, but emphasize that it can occur among those without ASA idiosyncrasy.

More of our subjects experienced worsening rather than improvement of their asthmatic symptoms and medication requirements during the avoidance diet, especially those having ASA idiosyncrasy (Table 6). The reasons for this lack of improvement and perhaps worsening of asthma are unclear. All subjects were well motivated and apparently adhered to the diet, but we cannot exclude the possibility of poor compliance. It is also possible that additives other than tartrazine or benzoate may have exacerbated asthma or masked any improvement, but as far as possible patients avoided all food additives. In addition, the rigidity of the avoidance diet did not appear to produce undue emotional stress. Moreover, the timing of the dietary assessment period did not coincide with any seasonal exacerbation of the subjects' asthma, except in one subject. Similarly the lack of improvement on the elimination diet cannot be ascribed to upper respiratory-infections as these occurred more commonly during the normal-diet period.

One further factor which has not been excluded as a cause for the apparent failure of the modified diet, is the possible effect of 'desensitization' to these substances. It has been reported that ASA idiosyncratic patients may become refractory to the adverse effects of aspirin by daily ingestion of ASA, and this state may persist for 3–7 days following the last ingestion of ASA (Zeiss & Lockey, 1976; Stevenson, Simon & Mathison, 1980; Pleskow *et al.*, 1980). No similar studies have been reported with tartrazine or benzoate but if the mechanism of the idiosyncratic response to these materials is speculated to be the same as that to ASA, then a similar refractory-state may occur. An avoidance diet would then obviate the induced refractory-state and occasional ingestion of even small amounts of tartrazine or benzoate in such a patient might produce an even greater response than similar ingestion while on a normal diet. This phenomenon may also explain the variable frequency of positive challenge-results obtained in different studies, since the practice of restricting the use of food additives prior to performing the test is neither uniformly applied nor followed for a sufficient interval. Further investigation is needed to determine whether there is a desensitization to the effects of tartrazine or benzoate in subjects with idiosyncratic responses. If there is, then challenge testing after a longer additive-avoidance period may give a better indication of the true frequency of tartrazine and benzoate idiosyncrasy. Moreover, the occurrence of desensitization may require that exposure to these materials be sustained since periodic ingestion may prove more harmful.

Asthma is well-known to vary for known and unknown reasons over short periods of time and thus the relatively small number of patients included in this study is not sufficient to confidently attribute the foregoing unexpected results to the dietary manipulations. Nevertheless the striking lack of advantage during the elimination diet in asthmatics who were considered ASA idiosyncratic by history or challenge or who had chronic disease but were not known to be idiosyncratic, suggests that this form of dietary avoidance used empirically is not likely to be helpful in the management of such

patients. Use of the elimination diet even in subjects who responded to challenge with tartrazine and benzoate was not of clear benefit.

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