

Oral tartrazine challenge in childhood asthma: effect on bronchial reactivity

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Summary

Ten asthmatic children who gave a history of cough or wheeze after orange drinks, were tested for tartrazine sensitivity. On separate days, either oral tartrazine (1 mg) or a placebo capsule were administered double blind. Bronchial reactivity was measured before, 30 and 60 min after ingestion by means of a histamine-inhalation challenge test. There was no change in baseline lung function after tartrazine, but histamine sensitivity (PC_{20}) increased significantly in four of the children. No response was obtained to a larger dose of tartrazine (10 mg) in four of the non-responders. Alteration in the bronchial reactivity after an oral challenge, appears to be a sensitive means of detecting tartrazine sensitivity.

Introduction

Tartrazine is a widely used colouring agent in many foods and beverages. In a recent survey of nineteen brands of orange drink on sale in London (Freedman, 1977), all were found to contain tartrazine, the dose of tartrazine contained in 250 ml of the appropriately diluted drink varying between 0.87 and 8.25 mg.

The importance of tartrazine in inducing asthmatic attacks in certain sensitive adults is well recognized (Lockey, 1959; Chaffee & Settiple, 1966; Samter & Beers, 1968; Stenius & Lemola, 1976). The incidence of tartrazine sensitivity in adult asthma varies between 0 and 22% (Table 1). The only double blind study in children (Vedanthan *et al.*, 1977) failed to demonstrate any change in forced expiratory flow after a large oral dose of tartrazine had been administered, perhaps because an inappropriate measurement of lung function had been made.

Changes in forced expiratory parameters will only indicate severe reactions to tartrazine. Recently, it has been shown that when sensitive individuals are exposed to certain allergens (Cockcroft *et al.*, 1977b) or food substances (Wilson *et al.*, 1982),

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Table 1. Reported incidence of adverse response to oral tartrazine in asthmatic patients

Investigator	No. of subjects	Method	Tartrazine dose (mg)	Criteria for positive test	Incidence (%)
Vedanthan <i>et al.</i> , (1977)	54*	Double blind	25	Fall in FEF ₂₅₋₇₅ > 2 s.d. of placebo group	0
Stenius & Lemola (1976)	114†	Open	0.1, 1.0, 10	PEF fall 20%	22
Freedman (1977)	10†	Open	20	FEV ₁ fall 12%	10
Spector <i>et al.</i> , (1979)	227†	Double blind	1, 5, 15, 25, 50	FEV ₁ fall 20%	4
Tarlo & Broder (1982)	27†	Double blind	1.5, 15	FEV ₁ fall 20%	4
Settipane & Pudupakkam (1975)	34†	Double blind	0.22, 0.44	FEV ₁ or PEF fall 20%	9

* Children.

† Adults.

enhanced bronchial reactivity may occur without detectable alteration in baseline lung function. The significance of increased bronchial sensitivity is clear: other trigger factors may more easily provoke an attack of asthma.

A number of children attending our asthma clinic gave a history of wheeze and cough after ingesting orange drinks. In a group of these children, we assessed the effect of tartrazine on peak expiratory flow (PEF) and bronchial sensitivity to histamine in a controlled, double-blind challenge.

Patients and methods

Ten asthmatic children giving a history of cough and wheeze after orange drinks were selected. Their mean age was 11.5 years (range 7–16) and six were boys. They attended the laboratory on two consecutive days, at the same time of day on each occasion. Beta-agonists were discontinued for at least 8 hr and sustained release aminophylline and sodium cromoglycate for 24 hr before each study period. None of the subjects were taking antihistamine preparations.

Subjects were given the test substance (tartrazine 1 mg) or an identical placebo capsule double blind, in random order. A standard protocol was used on each of the two study days. After baseline PEF had been recorded using a Wright peak flow meter (the maximum value of three attempts was accepted), a histamine challenge was performed after the method described by Cockcroft *et al.*, (1977a). Following the 2-min inhalation of a control solution of 0.9% saline, increasing concentrations of histamine were inhaled for 2 min each, at 5-min intervals, from a Wright's nebulizer. The PEF was recorded 30, 90 and 120 sec after the end of each inhalation. The procedure continued using doubling concentrations of histamine (0.063–16 mg/ml) until at least a 20% fall in PEF from the control value had been recorded. A dose-response curve was constructed and the dose which caused a 20% fall in PEF calculated (PC₂₀) by interpolation. Thirty min after the first histamine challenge a test capsule was given. This was followed by serial measurements of PEF for a further 30 min when a second histamine challenge was performed in a manner identical to the

first. In those subjects who did not respond to the oral challenge with a fall in PC_{20} of at least 50% from the control value, a third histamine challenge test was carried out after a further 30 min.

On completion of the two days of measurements, five of the six children who had had less than a two-fold difference in PC_{20} between the two test days, were given a single-blind oral dose of tartrazine 10 mg followed by a further histamine challenge.

The reproducibility of PC_{20} was assessed from the pairs of values before and after placebo challenge. From the ratio of pairs of values of PC_{20} measured 30 min before and after the placebo capsule, the confidence limits pairs of values of PC_{20} were estimated.

Results

There was no change in baseline PEF after oral tartrazine or placebo (Table 2). The values of PC_{20} before and after the placebo capsule were almost identical (Table 3). The

Table 2. Peak flow rate (l/min) at each stage of the study (mean $\pm$ s.d.)

	Placebo	Tartrazine
Before first histamine test	295 (100)	307 (110)
Before oral challenge	294 (98)	289 (96)
Before second histamine test	300 (96)	293 (112)

No difference reached statistical significance on paired *t*-test

Table 3. Histamine PC_{20} (mg/ml) before and 30 mins after each test capsule

Patient	Placebo		Tartrazine (1 mg)	
	before	after	before	after
1	2.60	2.40	1.48	0.5
2	16.0	16.0	10.0	3.47
3	1.30	1.10	1.80	0.36
4	1.10	1.15	0.50	0.35
5	13.5	14.0	16.0	14.2
6	2.40	2.50	2.40	2.80
7	6.0	7.0	16.0	16.0
8	2.50	2.45	1.40	1.50
9	2.25	2.85	2.60	2.40
10	1.20	a	1.30	a
Mean value ^b	3.4	3.5	3.1	c 2.0
s.d.	2.5	2.5	3.1	3.9

a, change in baseline PEF of 36 and 18% after placebo and tartrazine challenge precluded testing; b, after log transformation; excluding patient 10; c, difference significant on paired *t*-test of log PC_{20} ($P=0.05$).

mean ratio PC₂₀ before placebo/PC₂₀ after placebo was 0.98 mg/ml (s.d. 0.11). From these statistics, we estimated the confidence limits for the ratio of two tests, performed at a 1-hr interval, to be ± 0.22 mg/ml. Using these criteria, bronchial reactivity was enhanced by tartrazine 1 mg in four children, although in one case (4) the change was small. Overall, there was a statistically significant reduction in PC₂₀ after tartrazine ($P < 0.05$), but not after placebo.

Four patients (Nos 6–9) who failed to respond to 1 mg tartrazine at 30 min also had an unchanged PC₂₀ 60 min after ingestion. The same four patients, when challenged with 10 mg of tartrazine, failed to show any increase in bronchial sensitivity to histamine.

No adverse clinical reaction (wheezing, blocked nose, or urticaria) was noted in any patient. However, patient 10 wheezed at 30 min after ingestion of tartrazine and placebo. Her baseline lung function was so unstable that we were unable to complete the tests.

Discussion

This study examined the effect of tartrazine on bronchial reactivity in a group of children sensitive to orange drinks. Bronchial sensitivity to histamine increased in four patients 30 min after tartrazine ingestion, but not after placebo. Increased bronchial reactivity occurred in our patients without significant changes in PEF. This dissociation suggests that PC₂₀ is a more sensitive test of food sensitivity than is the PEF. A similar dissociation had been noted by Wilson *et al.*, (1982) in a group of children sensitive to cola drinks, while Cockcroft, *et al.*, (1977b) noted an increase in bronchial reactivity for up to 7 days, without change in baseline FEV₁ following an allergen inhalation test.

The value of double-blind and placebo testing has been emphasized by various workers (Settipane & Pudupakkam, 1975; Weber *et al.*, 1979; Tarlo & Broder, 1982). Frequency of positive results using open trials were higher (16–22%) (Stenius & Lemola, 1976; Weber *et al.*, 1979) than double blind studies (Table 1). Consistent with this interpretation, Weber *et al.*, (1979) found a 16% incidence of tartrazine sensitivity following challenge with an open design which reduced to nil when the same subjects were challenged using the double-blind method. One possible explanation for the higher incidence could be due to bronchial lability resulting from withholding medication. This effect was shown by patient 10 in our study who had an 18% and 36% fall in PEF on the two study days. This fall in PEF was almost certainly due to the waning of medication in a child with severe asthma, who required intensive therapy for adequate control. Thus, had a placebo preparation not been used, the fall in PEF could easily have been attributed to tartrazine or another challenge agent. Clearly this is a problem in severe asthmatics. One way of overcoming the problem would be to test such patients without withholding medication (Weber *et al.*, 1979; Tarlo & Broder, 1982). Although this could mask a minor degree of reactivity, in the severe asthmatic it may abolish the positive response to placebo which makes the results uninterpretable.

The change in bronchial reactivity occurred at 30 min, and the fact that the tartrazine was in capsule form makes it unlikely that inhalation of tartrazine was a factor in inducing the increase in non-specific bronchial reactivity. Dose does not appear to be important because in those patients not responding to 1 mg of tartrazine, a 10-fold increase in dose did not change bronchial reactivity in our study. However it is possible that a dose larger than 10 mg may have affected bronchial sensitivity. We

were guided by the survey done by Freedman which showed a tartrazine content up to 8.25 mg/250 ml orange drink. Increasing dose of tartrazine may be important as Spector, Wangaard & Farr (1979) found three patients responded to 1 mg, five patients to 5 mg, 1 patient to 15 mg and two patients to 25 mg, although high doses such as these may not be clinically realistic. Another possible explanation for our failure to demonstrate changes in bronchial reactivity to tartrazine in six of the children is provided by Freedman (1977). In most of his orange-drink-sensitive patients, the preservatives (sodium metabisulphate and sodium benzoate) were the responsible agents.

Adverse reactions to tartrazine in asthmatic patients have thus far been studied monitoring changes in forced expiratory flows. Thus the only study in children (Vedanthan *et al.*, 1977) failed to identify any tartrazine sensitivity. Using PEF changes we would have reached similar conclusions. However, using a more subtle test we have demonstrated that tartrazine increased bronchial sensitivity in four of the patients studied. The effect of increased bronchial reactivity in asthmatics is clear: other stimuli, such as exercise, cold air, allergen exposure or respiratory-tract infections, could more easily provoke asthmatic attacks. This study also draws our attention to the importance of ingested agents in increasing bronchial sensitivity in certain selected groups of childhood asthmatics.

References

- CHAFFEE, F.H. & SETTIPANE, G.A. (1966) Asthma caused by F.D. and C. approved dyes. *Journal of Allergy*, **40**, 65.
- COCKCROFT, D.W., KILLIAN, D.N., MELLORS, J.A. & HARGREAVE, F.E. (1977a) Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clinical Allergy*, **7**, 235.
- COCKCROFT, D.W., RUFFIN, R.E., DOLOVICH, J. & HARGREAVE, F.E. (1977b) Allergen induced increase in non allergic bronchial reactivity. *Clinical Allergy*, **7**, 503.
- FREEDMAN, B.J. (1977) Asthma induced by sulphur dioxide, benzoate and tartrazine contained in orange drinks. *Clinical Allergy*, **7**, 407.
- LOCKEY, S.D. (1959) Allergic reactions to F.D. and C. yellow No. 5 tartrazine, an aniline dye used as a colouring and identifying agent in various steroids. *Annals of Allergy*, **17**, 719.
- SAMTER, M. & BEERS, R.F. (1968) Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Annals of Internal Medicine*, **68**, 975.
- SETTIPANE, G.A. & PUDUPAKKAM, R.K. (1975) Aspirin intolerance. III. Subtypes, familial occurrence and cross-reactivity with tartrazine. *Journal of Allergy and Clinical Immunology*, **56**, 215.
- SPECTOR, L.S., WANGAARD, C.H. & FARR, R.S. (1979) Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *Journal of Allergy and Clinical Immunology*, **64**, 500.
- STENIUS, B.S.M. & LEMOLA, M. (1976) Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. *Clinical Allergy*, **6**, 119.
- TARLO, S.M. & BRODER, I. (1982) Tartrazine and benzoate challenge and dietary avoidance in chronic asthma. *Clinical Allergy*, **12**, 303.
- VEDANTHAN, P.K., MENON, M.M., BELL, T.D. & BERGIN, D. (1977) Aspirin and tartrazine oral challenge: incidence of adverse response in chronic childhood asthma. *Journal of Allergy and Clinical Immunology*, **60**, 8.
- WEBER, R.W., HOFFMAN, M., RAINE, D.A. & NELSON, H.S. (1979) Incidence of bronchoconstriction due to aspirin, azo dyes, non azo dyes and preservatives in a population of perennial asthmatics. *Journal of Allergy and Clinical Immunology*, **64**, 32.
- WILSON, N., VICKERS, H., TAYLOR, G. & SILVERMAN, M. (1982) An objective test for food sensitivity in asthmatic children: increased bronchial reactivity after 'cola' drinks. *British Medical Journal*, **284**, 1226.

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