Archives of Disease in Childhood 1992; **67**: 709–711

Tartrazine in atopic eczema

J Devlin, T J David

Abstract

Multiple double blind placebo controlled challenges with tartrazine 50 mg (three challenges) and glucose placebo (three challenges) were performed in 12 children with atopic eczema aged 1 to 6 years. The children were selected on the basis of severity (regular clinic attenders) and a parental history that tartrazine provoked worsening of the eczema. In only one patient did the three tartrazine challenge periods correspond with the highest symptom scores or the highest physician observer scores, and the probability of this occurring by chance in one or more patients out of 12 was 0·46. In this sample we were unable to confirm intolerance to tartrazine in 11 out of 12 patients.

Tartrazine and other artificial food colourings have been reported to provoke asthma[1 2] and urticaria[3] in susceptible individuals. Van Bever *et al* reported adverse reactions in all of six children with severe atopic eczema challenged with food additives, including two to tartrazine.[4] However, the severity of the reaction was not reported, and the reactions were all of an immediate skin flare type as the observation period of four hours did not allow for the detection of late reactions.

Day to day fluctuation in disease severity, which is a notable though unexplained feature of atopic eczema, and difficulty in objectively quantifying the disease, greatly hinder the interpretation of challenge tests. This is in contrast to other atopic disorders, where an endpoint (for example >25% fall in forced expiratory volume in one second) is more easily defined. Thus, challenge tests in which a single dose of food additive is compared with a single dose of placebo may give a positive result (that is worsening of eczema) in 50% of trials by chance alone. To investigate the effect of tartrazine on atopic eczema, we have therefore used multiple double blind placebo controlled challenges to increase the specificity of the test.

Department of Child Health, University of Manchester
J Devlin
T J David

Correspondence to:
Professor T J David, University Department of Child Health, Booth Hall Children's Hospital, Charlestown Road, Blackley, Manchester M9 2AA.

Accepted 7 February 1992

Patients and methods

All patients were attending the University Department of Child Health for treatment of atopic eczema, and all fulfilled the diagnostic criteria of Hanifin and Rajka.[5] There was no age limit for entry, but the children had to be able to drink from a straw. Thirty three consecutive patients with atopic eczema severe enough to require outpatient visits every three months were invited to participate in the study. Twenty three were already on a diet, supervised by a dietitian, which excluded tartrazine and other artificial colours and preservatives because of parental reports of intolerance to tartrazine and other additives. Of these 23, the parents of 16 declined because of fear that tartrazine would exacerbate the child's condition. Ten were started on such a diet, under the supervision of a dietitian, for the purposes of this study. Of these 10, four were excluded from the study because their parents considered that there had been no benefit from the diet. Thus 13 patients (nine boys, four girls; median age 3·8 years; range 1·9–6·9 years) entered the study. The median duration of eczema in these patients was 33 months (range 20–80 months). Seven patients were on an otherwise normal diet, five were excluding one or two foods believed to cause deterioration in their eczema, and one was on a trial of a few food diet. All patients were using topical corticosteroids. Eight used topical hydrocortisone (mildly potent, British National Formulary[6] (BNF) category IV), three used moderately potent (BNF category III) topical steroids, and two used potent (BNF category II) topical corticosteroids. The study was approved by the North Manchester Health Authority ethical committee and informed consent was obtained in each case.

The study period comprised three placebo and three active weeks in random order. There are 20 (6!/3!3!) possible permutations of three placebo and three tartrazine weeks. The regimen for each patient was randomised at entry by the pharmacist drawing a sealed envelope from a shuffled pack containing equal numbers of each permutation. Six gelatine capsules, each containing either tartrazine 50 mg or glucose placebo 50 mg, were supplied in opaque glass bottles numbered corresponding to the order of administration. On the first day of each week, between 8·30 and 11 am the patient attended the ward. Each patient attended at the same time each week. The contents of the appropriate capsule were dissolved in pure orange juice and administered by a nurse to the patient, who drank the juice through a straw from a sealed opaque plastic cup.

The percentage surface area affected by eczema was assessed using a chart similar to one used for recording the surface area of thermal injuries (table 1), and the severity of erythema by a numerical scale from 1 (mild) to 5 (severe). An overall combined severity score was obtained by multiplying the percentage surface area by the erythema score. The assessment was performed by a single observer (JD), immediately before the administration of the

Table 1 Assessment of eczema extent

	Demarcation	*% Surface area*
Face+scalp	Anteriorly, angle of jaw; posteriorly, hairline	14
Neck	Anteriorly, jaw to upper border clavicles; posteriorly, hairline to line between acromion tips	4
Right arm	Acromion tip to two finger breadths above ulnar head	7
Left arm	Acromion tip to two finger breadths above ulnar head	7
Right hand	Distal to two finger breadths abover ulnar head	4
Left hand	Distal to two finger breadths above ulnar head	4
Trunk	Clavicles to line between ASIS	10
Back	From line between acromion tips to line between ASIS	12
Pelvis	From line between ASIS to pubic tubercles	4
Buttocks	From line between ASIS to gluteal folds	6
Right leg	From line joining ASIS and pubic tubercles anteriorly and from gluteal folds posteriorly to three finger breadths above medial malleolus of tibia	10
Left leg	From line joining ASIS and pubic tubercles anteriorly and from gluteal folds posteriorly to three finger breadths above medial malleolus of tibia	10
Right foot	Area distal to three finger breadths above medial malleolus of tibia	4
Left foot	Area distal to three finger breadths above medial malleolus of tibia	4

ASIS=anterior superior iliac spines.

tartrazine or placebo, and again 24 to 48 hours later, and the change in score (increase or decrease) was used as the parameter for analysis.

The parents were asked to keep a record of symptoms—severity of itch, skin redness, night time disturbance, urticaria, itchy or runny nose, wheeze, and behaviour problems—on a scale of zero (no problem) to 10 (very severe), each day for seven days after the administration of the capsule. For each week, a mean daily score for each symptom was calculated. A combined eczema symptom score was derived by summing the mean daily scores for itch, redness, and nocturnal disturbance with a maximum possible score of 30. A positive challenge was defined as one in which the three tartrazine weeks corresponded either to the three with the highest symptom scores or to the three with the greatest increase in severity score, the probability of such a correspondence being 0·05 for each comparison.

Data were analysed for results on individual subjects to determine the frequency of positive challenges, and the tartrazine and placebo weeks were compared for the group as a whole.

Results

Challenges were abandoned in one patient who moved from the area after the second challenge. The data from the remaining 12 patients were analysed.

Table 2 Details of eczema symptom and severity scores

Patient	*Mean daily symptom scores*		*Change in severity score after capsule*	
	Tartrazine	*Placebo*	*Tartrazine*	*Placebo*
A	2, 5·1, 10	3·3, 5·4, 9·7	0, 0, 0	0, 0, 0
B	15·1, 15·4, 13·7	11·3, 14·3, 16	0, +68, −33	−38, +12, +2
C	23·7, 23·7, 25·4	23·3, 25·4, 25·9	+25, +27, 0	+2, −2, −18
D	7, 4·3, 9	6·4, 5·4, 8·1	+6, +3, −1·5	+2·5, +1, −8·5
E	9·7, *, 17·9	12·9, 6·6, 10·7	0, 0, +12	0, −108, +28
F	10·4, 6·9, 4·9	5·9, 4·7, 5·7	0, −23.5, 0	−12, 0, +16
G	0·9, 2·1, 0	0·3, 7·4, 1·9	0, 0, −10·5	0, −3, 0
H	17·1, 13, 12	*, 14·1, 18·3	+63, +73, −4	0, +73, +62
I	9·3, 15·3, 14·9	4·6, 4·3, 11·4	−5, 0, −16	0, 0, −16
J	9, 7·3, 10·1	7·, 10·9, 8·9	0, 0, −21	0, −26, +2
K	11, 13·1, 11	11·9, 11·6, 6·4	0, +14, −28	−4, −4, 0
L	10·9, 10·9, 14·9	9·3, 9·4, 9·3	+32, +21, +3	0, +2, −14

*Data not available (see text).

INDIVIDUAL DATA

Eczema

Two of the 12 patients who completed the study period lost their diary cards for one week, but there were sufficient symptom score data from the other five weeks to exclude a reproducible reaction to tartrazine and these patients were regarded as negative challenges (table 2).

In one of the 12 patients (patient L) the three tartrazine challenges corresponded with the three weeks which had the highest symptom score and also with the three weeks which had the greatest increase in observed eczema severity. There was no such correspondence in either symptom or disease severity score in any of the other 11 patients. According to the binomial theorem, in N independent trials, where the probability of an event occurring in each trial is p, the probability that the event will be observed in at least k trials is given by[7]:

$$1-\sum_{0}^{k-1}\frac{N!p^{x}(1-p)^{N-x}}{x!(N-x)!}$$

Given that the probability of the three worst weeks of six corresponding to the three tartrazine weeks by chance in a single patient is 0·05, the probability of this occurring in one or more patients out of 12 is 0·46.

Other symptoms

In one patient (G) the three worst weeks for wheeze and the three worst for rhinitis corresponded to the three tartrazine weeks. No other patient showed positive challenges for these symptoms. Three patients each had a single episode of urticaria, each occurring during a tartrazine week. No patient showed behavioural changes related to tartrazine administration.

GROUP DATA (TABLE 3)

Eczema

The total daily eczema symptom scores for the three tartrazine weeks were combined and compared with those for the placebo weeks in each of the 10 patients for whom full data was available (parents' data were missing in two subjects). Although the median score for the tartrazine weeks (216) was higher than that for the placebo weeks (154), the difference was not significant ($p>0·1$, Wilcoxon signed rank test). The changes in eczema severity score were summed for the three tartrazine weeks and compared with the summed changes in the placebo weeks for all 12 of the patients. Again, although the median change in score was higher in the tartrazine weeks (+4) than in the placebo weeks (−6), the difference was not significant ($p>0·1$, Wilcoxon signed rank test).

Other symptoms

Similarly, the total symptom scores for wheeze, rhinitis, and behaviour for the three tartrazine weeks were compared with those for the placebo weeks in each of the 10 patients for whom full data were available. No significant difference

Table 3 Group results combining three tartrazine and three placebo weeks

Patient	Mean daily symptom scores for:								Mean change in severity‡ 24 hours after challenge given	
	Eczema*		Rhinitis†		Wheeze†		Behaviour†			
	Tartrazine	Placebo	Tartrazine	Placebo	Tartrazine	Placebo	Tartrazine	Placebo	Tartrazine	Placebo
A	5·7	6·1	0·3	1·0	0	0	1·3	1·7	0	0
B	14·8	13·9	0·2	0·5	0	0	0	0	+12	−8
C	24·3	24·9	5·5	5·0	7·6	7·3	6·0	5·6	+8	+4
D	7·4	6·7	0	0	0	0	0	0	+2	−2
E	NA	NA	NA	NA	NA	NA	NA	NA	+4	−27
F	7·4	5·4	1·4	0·9	0	0	0·3	0	−8	+1
G	1·0	3·2	0	0·3	0·2	0·3	0·2	0·4	−4	−1
H	NA	NA	NA	NA	NA	NA	NA	NA	+44	+45
I	13·1	6·8	2·7	2·0	3·0	2·0	3·1	1·4	−7	−5
J	8·8	8·0	0	0	0	1·4	3·1	2·7	−7	−8
K	11·7	10·0	4·4	3·6	3·5	3·4	2·1	2·1	−5	−3
L	12·2	9·3	3·0	3·4	0	0	3·2	4·0	+18	−4

*Maximum score 30, †maximum score 10.‡ Plus sign denotes deterioration, minus sign denotes improvement. NA=data not available.

was found for any of these symptoms ($p>0·1$, Wilcoxon signed rank test).

Discussion

This project was designed to try to overcome the difficulties encountered in studying a disease which is difficult to quantify objectively and which is characterised by unpredictable fluctuation in severity. Our method can be assumed to have a 'false positive' rate of 5%, and so cannot be used to screen a population with a very low prevalence of additive intolerance. One problem in the interpretation of this study is that the improvement obtained on the artificial colouring and preservative free diet could in theory have been due to the exclusion of an additive other than tartrazine, notwithstanding parental observation of intolerance to tartrazine. To investigate the possibility of intolerance to other additives would have been impractical. For example, to have studied only 10 other additives would have required weekly attendance at hospital for a further 60 weeks. We chose to investigate a single azo dye, tartrazine, because this commonly used food colouring is one of those most frequently implicated in adverse reactions, and because the parents of the subjects in the study believed their child to be intolerant to tartrazine. There is an hypothetical argument that as the mechanism of tartrazine intolerance is unknown, the timing of an adverse reaction cannot be predicted and might appear towards the end of an 'active' week or even in the next week. To detect such delayed reactions would require a wash-out period of arbitrary duration after each active week to prevent contamination of 'placebo' weeks. Against this argument is the observation from double blind placebo controlled challenge studies that adverse reactions to tartrazine were almost immediate and occurred within three to four hours after ingestion.[3 8 9]

In only one patient of the 12 studied was there a clear correspondence between tartrazine administration and worsening of eczema, as assessed both by symptoms and clinical examination, but, as explained above, this would have been expected by chance alone. A second patient had wheeze and rhinitis symptoms which correponded to tartrazine weeks. We also sought, but failed to find, evidence of a more subtle effect of tartrazine administration, not detectable in an individual subject but evident in the group as a whole.

The mechanism by which tartrazine might cause deterioration in eczema remains obscure. Our one patient who appeared to react consistently showed an objective worsening in her skin when examined clinically, approximately 24 hours after each dose of tartrazine and lasting for three to four days. Her parents did not notice any urticarial lesions.

Reluctance to participate in the study for fear of adverse reaction was a problem when recruiting patients, in contrast to the ease we have experienced in finding patients willing to try new possibly beneficial treatments. It is possible that, as with behavioural problems attributed to tartrazine,[10] parental anxiety about the adverse effects of tartrazine in atopic eczema may be disproportionate.

We would like to thank Mr J Lockwood, principal pharmacist, Booth Hall Children's Hospital, for preparing the capsules and randomising the patients, and the nursing staff of Ward 4 for their help. JD was supported by the National Eczema Society.

1 Morales MC, Basomba A, Pelaez A, Garcia Villalmanzo I, Campos A. Challenge tests with tartrazine in patients with asthma associated with intolerance to analgesics (ASA-triad). *Clinical Allergy* 1985;**15**:55–9.
2 Hariparsad D, Wilson N, Dixon C, Silverman M. Oral tartrazine challenge in childhood asthma: effect on bronchial reactivity. *Clinical Allergy* 1984;**14**:81–5.
3 Supramaniam G, Warner JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986;**ii**:907–9.
4 Van Bever HP, Docx M, Stevens WJ. Food and food additives in severe atopic dermatitis. *Allergy* 1989;**44**:588–94.
5 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatovener* 1980; suppl **92**:44–7.
6 British Medical Association and the Royal Pharmaceutical Socieity of Great Britain. *British national formulary*. No 20. London: BMA and the Royal Pharmaecutial Society of Great Britain, 1990:364.
7 Documenta Geigy. *Statistical methods*. 7th Ed. 1970. (Equations 97, 373, 744.)
8 Settipane GA, Pudupakkam RK. Aspirin intolerance. III. Subtypes, familial occurrence, and cross-reactivity with tartrazine. *J Allergy Clin Immunol* 1975;**56**:215–21.
9 Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;**64**:500–6.
10 David TJ. Reactions to dietary tartrazine. *Arch Dis Child* 1987;**62**:119–22.