Adverse reactions to tartrazine

R.H. LOBLAY and A.R. SWAIN

Adverse reactions to tartrazine may cause symptoms involving the skin (urticaria and angioedema, eczema), gastrointestinal tract, respiratory tract and/or central nervous system. Susceptibility appears to be familial, and more widespread than is generally appreciated. There is strong circumstantial evidence that reactions are pharmacological in nature rather than immunological, and specific sensitisation by ingestion is therefore unlikely. Reactions appear to be dose-related, and sensitive patients may exhibit withdrawal reactions and supersensitivity, as well as tachyphylaxis and tolerance after reintroduction. There is extensive cross-reactivity between tartrazine and other dyes we have tested, and also between azo-dyes and other food chemicals. These include not only various preservatives and flavourings, but also natural compounds such as salicylates and amines. Overall, natural salicylates are the single commonest substance to produce reactions when tested by double-blind oral challenge. Most patients are sensitive to multiple substances (between 2 and 10 commonly), and the effects can be additive. It is not known as yet whether there is synergy between specific compounds.

Adverse reactions to tartrazine were first documented in the late 1950s, and are currently recognised as being capable of provoking asthma, urticaria, angioedema and systemic anaphylactoid reactions in sensitive patients (MacCara 1982). The incidence of such reactions is not known with precision, but recent estimates range between 1:1000 and 1:10 000 (Anon. 1980, Juhlin 1980). Public interest was stimulated during the 1970s by Feingold's claims that 'hyperactivity' in children were commonly precipitated by tartrazine and other food additives (Feingold 1975); this together with continuing case reports in the medical literature has led to the introduction of legislation aimed at improving the labelling of processed foods.

It has also been recognised that there is a degree of cross-reactivity between aspirin and tartrazine in up to 20% of patients with aspirin intolerance, which has led to speculations that tartrazine may act by the inhibition of cyclo-oxygenase and prostaglandin formation. However, recent studies have failed to support this hypothesis (Gerber *et al.* 1979, Moneret-Vautrin & Martin 1985) and at present the mechanism of adverse reactions is uncertain.

Thus, a review of the recent literature shows that despite recognition over 25 years ago, there is still no clear understanding of the epidemiology, clinical spectrum, range of cross-reactivity or mechanism of tartrazine intolerance. The purpose of the present communication is to put adverse reactions to tartrazine into perspective against the broader problem of food intolerance in its many guises so as to provide a sound clinical basis for future research.

Patients

An elimination diet and challenge program for the investigation of patients with food intolerance has been in operation at the Allergy Clinic at Royal Prince Alfred Hospital, Sydney, since 1977. This was initially designed to assist in the management of patients with chronic idiopathic urticaria and angioedema, and the results in 76 patients have been published previously (Gibson & Clancy 1980). Since that time the elimination diet has been modified as a result of clinical experience and extensive laboratory analyses of food salicylate levels (Swain, Dutton & Truswell 1985). The challenge battery has been expanded and made double-blind to allow more extensive and objective investigation of patients presenting with more subjective symptoms such as migraine, irritable bowel and central nervous system symptoms (Allen *et al.* 1984). Over 2000 patients with varying manifestations of food intolerance have now been investigated with this modified protocol; the results will be reported elsewhere.

Challenges

In the course of investigating 140 children with hyperactivity (Swain *et al.* 1985) it was noted that parents frequently incriminated red ice-blocks and green cordials as precipitating factors, and we decided to modify our routine challenge battery in order to compare the effects of different dyes and to determine whether they might have more potent effects in combination with preservatives. Four colouring challenges were included in the standard battery as follows: tartrazine (30 mg), erythrosine (30 mg), 'green' colour (tartrazine 24 mg, brilliant blue 6 mg) and 'cordial' ('green' colour 28 mg, sodium benzoate 80 mg, sodium metabisulphite 23 mg). These and 11 other standard challenge compounds (including placebos) were taken at 48 h intervals after a minimum of two weeks' strict elimination and five consecutive symptom-free days. Only those patients who experienced complete or substantial relief of symptoms on the elimination diet were tested by oral provocation; the protocol has been described in detail by Allen *et al.* (1984). A total of 78 consecutive patients with urticaria, migraine, irritable bowel syndrome, hyperactivity or systemic symptoms were tested with all four of the above colour challenges (administered in a random order) and symptoms were recorded in a diary. These challenges were not strictly double blind, since the coloured compounds were taken in clear gelatin capsules. However, in previously administered challenge batches we controlled for the yellow colour by using β -carotene as a placebo, or concealed the colour by placing the tartrazine capsule into a larger capsule filled with starch, and in both these situations there was no significant difference in the frequency of positive reactions to tartrazine. In

Dr Robert Loblay is in the Department of Clinical Immunology and Anne Swain is dietitian in the Department of Dietetics, The Royal Prince Alfred Hospital, Camperdown, NSW 2050.

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Table 1. Response to tartrazine challenge

Syndrome	Response rate (%)
Urticaria	20
Eczema	19
Migraine	32
Irritable bowel	23
"Hyperactivity"	33
Systemic	33

Table 2. Colouring challenge reactions (%)

Tartrazine alone	8
Erythrosine alone	27
Both	18
Neither	47

Table 3. Urticaria: challenge reactions

Patient	Tartrazine	Erythrosine	'Green'	'Cordial'
E.L.	+	+	+	+
M.W.	—	—	—	—
L.M.	—	—	—	—
A.H.	—	+	—	—
C.F.	—	—	—	—
C.G.	+	+	+	+
R.H.	—	—	—	—
A.M.	—	—	—	+
M.M.	+	+	—	—
H.M.	+	—	—	—
Y.S.	—	—	—	—
J.D.	—	—	—	+
B.B.	—	+	+	—
Total	*4*	*5*	*3*	*4*

Table 4. Migraine: challenge reactions

Patient	Tartrazine	Erythrosine	'Green'	'Cordial'
M.A.	—	+	—	—
P.B.	—	+	—	—
J.L.	+	—	—	—
J.M.	+	—	+	—
K.S.	—	+	—	—
S.T.	—	—	—	—
F.V.	—	—	—	+
R.D.	—	—	—	+
D.D.	—	—	+	+
D.B.	—	—	+	—
E.B.	—	—	—	—
R.Z.	—	—	+	—
J.B.	—	+	—	—
Total	*2*	*4*	*4*	*3*

Table 5. Hyperactivity: challenge reactions

Patient	Tartrazine	Erythrosine	'Green'	'Cordial'
C.K.	+	+	—	—
A.M.	—	+	+	+
A.B.	—	—	—	—
M.B.	—	+	+	+
N.C.	+	—	—	—
L.D.	—	—	+	—
D.F.	+	+	+	+
A.N.	+	+	+	+
A.S.	—	+	+	+
O.S.	—	—	—	+
A.S.	—	—	—	—
H.W.	+	—	+	—
M.I.	+	+	+	—
J.I.	—	—	+	—
Total	*6*	*8*	*11*	*7*

patients with urticaria no positive reactions were recorded with placebo challenges (Allen *et al.* 1984) and the placebo reaction rate in all other groups was less than 10%.

Results

Significant improvement of symptoms on the elimination diet occurred in between 43% and 70% of patients tested, depending on the presenting syndrome. Those who did not respond were allowed to resume a normal diet. The overall response rate to tartrazine challenge in each group is shown in Table 1; results are expressed as a proportion (%) of the total number of patients seen in each group, regardless of their response to the elimination diet. Symptoms provoked by challenges in those tested were generally those with which the individual patients originally presented, and there was no tendency for any particular challenge compound to produce any characteristic symptom or combination of symptoms.

In all patient groups there was a consistently higher response rate with salicylate challenges (up to 45%); this frequently co-existed with tartrazine reactions, confirming the previously reported high degree of cross-reactivity between these two compounds. Furthermore, most patients reacted to several other challenge compounds with the same symptoms, e.g. preservatives, antioxidants, amines, MSG, brewer's yeast, the pattern varying from one individual to another. The extent of reactivity varied with each group, patients with urticaria for example reacting on average to between 2 and 5 challenge compounds, whilst those with irritable bowel syndrome commonly reacted to between 4 and 10 challenges.

Results in the 78 patients given the four separate colour challenges are shown in Table 2. Thus, 53% of patients reacted to one or more dye. Of those sensitive to tartrazine, 70% were also sensitive to erythrosine; overall, reactions to erythrosine were nearly twice as common as those to tartrazine. Furthermore, of the 37 patients not reacting to either tartrazine or erythrosine, 10 (27%) reacted to the combination of tartrazine + brilliant blue. Individual patterns of responsiveness in consecutive patients with urticaria, migraine and hyperactivity are shown in Tables 3, 4 and 5, and demonstrate that there is a high degree of variability such that any permutation or combination may be observed. Moreover, there is also a high degree of cross-reactivity between azo-dyes and preservatives, as well as naturally occurring amines and salicylates, as shown in Tables 6, 7 and 8.

Discussion

Several conclusions can be drawn from the results presented above. First, it is clear that the clinical spectrum of adverse reactions to tartrazine is much broader than has been hitherto recognised. Reactions appear to represent an individual idiosyncracy, and the symptoms produced vary depending on the target organ susceptibility in each patient. The propensity to react to tartrazine and other natural as well as artificial food chemicals is probably genetically determined, as a family history of similar or related symptoms is very common. Indeed, we have studied 47 families in which two or more members (siblings, or one parent and one or more children) have undergone challenge testing. There is a strong tendency for family members to react

Table 6. Urticaria: challenge reactions

Patient	Azo-dye	Preservative	Salicylate	Amine
E.L.	+	—	+	+
M.W.	—	—	+	—
L.M.	—	—	—	—
A.H.	+	—	—	—
C.F.	—	—	+	+
C.G.	+	+	+	+
R.H.	—	—	+	—
A.M.	—	+	+	—
M.M.	+	—	+	+
H.M.	+	+	+	+
Y.S.	—	—	+	—
J.D.	—	+	+	+
B.B.	+	—	—	+
Total	*6*	*4*	*10*	*7*

Table 7. Migraine: challenge reactions

Patient	Azo-dye	Preservative	Salicylate	Amine
M.A.	+	—	—	+
P.B.	+	—	—	—
J.L.	+	+	+	+
J.M.	+	—	+	+
K.S.	+	—	—	—
S.T.	—	+	—	—
F.V.	—	+	+	—
R.D.	—	+	+	—
D.D.	+	—	+	—
D.B.	+	—	+	—
E.B.	—	+	+	—
R.Z.	+	—	—	—
J.B.	+	+	—	+
Total	*9*	*6*	*7*	*4*

Table 8. Hyperactivity: challenge reactions

Patient	Azo-dye	Preservative	Salicylate	Amine
C.K.	+	—	—	—
A.M.	+	—	+	+
A.B.	—	+	+	—
M.B.	+	+	+	—
S.B.	—	+	—	+
D.B.	+	—	+	—
M.B.	+	—	+	—
N.C.	+	+	+	—
L.D.	+	+	+	—
D.F.	+	+	+	+
A.N.	+	+	+	—
A.S.	+	—	+	—
O.S.	—	+	—	—
A.S.	—	+	—	—
H.W.	+	—	—	—
M.I.	+	+	—	—
J.L.	+	—	+	+
Total	*13*	*10*	*11*	*4*

to the same range of compounds, although the symptoms provoked may vary from one member to another.

Second, the extent of cross-reactivity between tartrazine and other dyes, and between tartrazine and a wide range of other natural and artificial food substances has not been fully appreciated. This carries important implications concerning the possible mechanism(s) of tartrazine intolerance, since many of these substances may be expected to have quite different metabolic effects, and are structurally unrelated to one another.

Finally, clinical observations in patients with documented food intolerance suggest that reactions to each of the relevant substances, including tartrazine, are dose-related. This has been confirmed recently in a double-blind study of tartrazine reactions in hyperactivity, where the Conners scale was used to quantify the severity of symptoms provoked in sensitive children (K.S. Rowe, pers. commun.). Furthermore, the chemicals incriminated commonly exhibit phenomena such as withdrawal reactions followed by supersensitivity, tachyphylaxis and tolerance. This, together with the lack of evidence of an underlying immunological mechanism, suggests that adverse reactions occur on a pharmacological rather than allergic basis.

Since natural food chemicals provoke symptoms more frequently than artificial additives, we believe there is no rationale for banning the use of food additives, although minimising the concentrations added to processed foods would be likely to reduce the frequency and severity of adverse reactions in sensitive individuals.

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Questions and discussion (edited) on adverse reactions to tartrazine

Question: What is the incidence of sensitivity to tartrazine in the Australian population?

Dr Loblay: No adequate epidemiological data are available to answer this question. To hazard a guess, on the basis of our experience the incidence may be as high as 10%, but I would qualify that by emphasising that there is a wide range of sensitivity. The majority of our patients require quite a large dose to provoke symptoms. Only a small minority are highly sensitive so that a small dose provokes severe symptoms.

Dr A.J. Ryan (Department of Pharmacy, University of Sydney): I have not worked in this field for many years but I believe we were the first to show that sulphanilic acid was one of the metabolites of tartrazine. There are several points that I would like to make. Most commercial dyestuffs contain some residual starting materials as Dr Pascual has stated, e.g. in tartrazine, p-sulpho-phenylhydrazine, and this substance is also a metabolite of tartrazine. Phenylhydrazine derivatives are well known to provoke allergic reactions. I am surprised that such starting materials and metabolites do not appear to have been tested in challenge trials. Most food colours are highly sulphonated and are very poorly absorbed from the gut. This makes it unlikely that the intact dyestuff is responsible for the reactions observed. I believe further investigation is necessary to discover what are really the causative agents. I would also point out that it is the microbial flora in the gut that is mainly responsible for the metabolic breakdown of food colours, not an endogenous system.

Dr Loblay: Thank you for those comments. If the breakdown products of food colours are the causative agents, that may explain the cross reactivities we have observed in adverse reactions to the colours and a number of substances of smaller molecular weight.

Dr Emerson: **Dr Loblay, how do you grade the behaviour of your subjects?**

Dr Loblay: Subjectively — we ask the mothers to keep a record of behaviour patterns. We have not used objective tests such as the Connors Scale because there is much controversy about their value. We rely heavily on the double-blind administration of the challenges to ensure the validity of the observations, and we are strongly supported in this by subsequent clinical experience and management of the children.

Dr Emerson: I am surprised at the high incidence of behaviour problems you have encountered; it is much higher than in controlled studies in the USA and Canada. Workers in Sweden have also reported a high incidence of behavioural reactions to foods, and an associated high incidence of eczema. Have you also found a high incidence of eczema?

Dr Loblay: Among 140 subjects we have studies with behaviour problems only two exhibited eczema. However in a recent London study where food challenges were found to provoke objective behaviour symptoms, 40% of the subjects showed eczema. There may well be a difference between countries in the incidence of eczema.

Speaking generally about conflicting reports in the literature about adverse reactions, our experience indicates that the nature of the base line diet is critical in relation to subsequent reactions to challenge. The basic diets used in published studies are widely varied and often they are very inadequately described.

Question: Do you distinguish between behaviour disturbance and hyperactivity?

Dr Loblay: The majority of our subjects with behaviour problems could be described as hyperactive. We realise only too well the difficulties in assessing the behaviour of children, in distinguishing true biological abnormalities from the effects of environmental or family influences. The assessment is done by a pediatrician and patients are enrolled in the clinic only if it is considered that a relevant problem exists. Nothing confirms the validity of such assessments more than the positive, often highly bizarre, reactions to challenge that we generally observe.

Question: Dr Loblay and Mrs Swain have described challenge studies in which control was provided by the double-blind design, but have they tried another form of control by challenging children judged to be normal?

Mrs Swain: In many cases the challenges are administered to all members of the family of a patient who presents with behavioural disturbance. In general those members of the family who have not previously experienced adverse reactions show no response to the challenge.

Dr Loblay: Another way to answer the question is to point again to the very specific symptoms shown by different groups of patients. Children who present with urticaria generally develop urticaria when challenged, but virtually never behaviour disturbance. Likewise, children who present with recurrent headaches develop neither urticaria nor behaviour problems when challenged but recurrent headaches. This is the phenomenon of target organ susceptibility already referred to. On the other hand, we have found a strong correlation between behaviour symptoms and the cluster of physical symptoms we have described. It is very rare to find a child who reacts with behaviour symptoms alone. The question remains unresolved as to whether the behaviour symptoms are provoked or aggravated by the physical symptoms.

Question: Why do you challenge with a mixture of the preservatives, benzoic acid and sulphite, rather than with the individual substances?

Mrs Swain: Essentially to make the challenge protocol shorter and less tedious for subjects, and also because these preservatives are often used together in foods. In the subsequent management of patients they may have to be told to avoid all foods with preservatives. But we do challenge separately with propionic acid and nitrate so that patients need not be put off bread and cured meats if it is not necessary.

Question: How can you study mechanisms of adverse reactions when you challenge with mixtures of substances that are unrelated chemically?

Dr Loblay: Our protocol is not aimed at the elucidation of mechanisms. The correct approach for that purpose is intensive study of small sub-groups of patients whose reactions are well documented; and such studies are in progress.

Question: If we accept that tartrazine may cause adverse reactions in sensitive individuals, what are the possibilities for food manufacturers to substitute another colour, or to use another colour in mixture with tartrazine to reduce the amount of that colour? For instance, are carotenoid colours or Sunset Yellow possible alternatives?

Dr Pascual: Sunset Yellow cannot replace tartrazine because it gives an orange colour. A lemon yellow colour which could replace tartrazine and which has a high ADI according to JECFA is Quinoline Yellow. This colour is permitted in the EEC but not in Australia. However a food manufacturer could make application for its use by the specified procedures. Carotenoid colours, such as β-carotene, have the disadvantages that they are insoluble in water, they cost about ten times as much as tartrazine, and they must be used at about five times the concentration.