

The danger of 'yellow dyes' (tartrazine) to allergic subjects

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Summary

Oral administration of 50 mg tartrazine to 122 patients with a variety of allergic disorders caused the following reactions: general weakness, heatwaves, palpitations, blurred vision, rhinorrhoea, feeling of suffocation, pruritus and urticaria.

There was activation of the fibrinolytic pathway as shown by reduction of plasminogen with high pre-kallikrein and low kallikrein values. Reduction in complement activity (CH_{50}) was seen in three out of sixteen reactions.

Introduction

Tartrazine (FD and C yellow No. 5) has been widely investigated in recent years (Stenius & Lemola, 1976; Lockey, 1959, 1977; Michaelsson & Juhlin, 1973; Settupane *et al.*, 1976; Smith & Slavin, 1976). Extremely large amounts of food additives are consumed all over the world (Prenner & Stevens, 1976). Pharmaceutical companies add the dye to colour and flavour medications (Smith & Slavin, 1976), and even drugs for the atopic population may contain these additives (Buswell & Lefkowitz, 1976).

Part of the atopic population show clinical reactivity to tartrazine, and it is suggested that the clinical symptoms may be due to enhanced bradykinin production, as one of the possible mechanisms involved.

Materials and methods

Ninety-seven patients with allergic disorders, and twenty-five without, were evaluated. The case history was taken, together with physical examination, blood and nasopharyngeal eosinophilia screening, sinuses and chest X-rays, pulmonary function tests and skin tests with forty-five environmental allergens. In patients with urticaria, Wood's lamp examination of the skin for presence of fungi was done, and tests for the effects of cold, heat, u.v. and mechanical pressure were made.

All patients were put on to a diet devoid of food additives for 1 week, and were taken off all medication 24 hr prior to a randomized single blind oral challenge with either 50 mg tartrazine or with 50 mg dextrose as placebo in gelatinous opaque

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capsules. Bleeding time was measured prior to and 10 min after challenge, by the method of Duke (Dacie & Lewis, 1970), the normal range being considered 1–4 min.

Blood was withdrawn for extensive laboratory investigations from four non-atopic controls, who did not react to the tartrazine challenge, and from sixteen patients with positive clinical reactions, 10 min after the administration of 50 mg tartrazine or placebo. In four of the patients who reacted to the dye, the challenge was repeated with 10 mg and blood was again taken.

The following measurements were made: immunoglobulin quantification by using self-made immunoplates with antiserum from Meloy Laboratories (Meloy, Springfield, Virginia 22151); normal laboratory levels were: 800–1800 mg/dl for IgG, 90–450 mg/dl for IgA and 60–250 mg/dl for IgM. The generation of kinins and the complement pathway were assayed as previously described (Neuman & Creter, 1977). Kallikrein inhibitor was determined by the method described by Colman, Mason & Sherry (1969) using arbitrary units, the normal laboratory range being considered more than 15 units. The fibrinolytic pathway study included the determination of fibrinogen by radial immunodiffusion with self-made immunoplates, using fibrinogen antiserum (Behringwerke AG, Marburg Lahn, West Germany) (Mancini, Carbonara & Heremans, 1965). The normal laboratory range was between 200 and 400 mg/dl. Euglobulin lysis time and plasminogen were determined as previously described (Neuman & Creter, 1977).

Table 1. Incidence of reactivity to tartrazine

Diagnosis	Total patients	Positive reaction	Percentage
Urticaria	30	7	23
Angioedema	4	0	0
Allergic rhinitis and asthma	41	16	39
Drug and food hypersensitivity	11	7	64
Pruritus	5	1	20
Insect bite hypersensitivity	5	1	20
Sub-total, allergic population	97	32	33
Vasomotor rhinitis, non-atopic	25	0	0
Total	122	32	26

Results

Table 1 presents all 122 patients challenged with tartrazine ingestion and the distribution of the clinical allergic diagnosis. In thirty-two patients, that is 26%, positive reactions occurred 10–15 min after the challenge. Thirteen of the positive patients (40%) complained of a heat-wave, general weakness and blurred vision. Six patients (19%) had increased nasopharyngeal secretions, a feeling of suffocation and palpitations, and another six (19%) had pruritus, urticaria or both. In six cases (19%), a prolongation of the bleeding time was observed, though within normal limits. 3% of the patients had angioedema.

Immunoglobulins, represented in Table 2, were normal in all patients. However, while remaining within the normal range, a drop was observed after tartrazine challenge, especially in the immunoglobulins G and M.

Table 2. Immunoglobulin determination

Challenges	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)
Normal laboratory range	800-1800	90-450	60-250
Dye challenge	1034 $\pm$ 71.85	284 $\pm$ 33.34	141 $\pm$ 21.90
Placebo challenge	1266 $\pm$ 77.98	255 $\pm$ 51.88	203 $\pm$ 45.38

All results mean $\pm$ s.e.m.

Table 3. Fibrinolysis pathway

Challenges	Fibrinogen (mg/dl)	Euglobulin lysis time (hr)	Plasminogen (mg/dl)
Normal laboratory range	200-400	> 2	10-22
Dye challenge	320.00 $\pm$ 9.68	> 2	8.62 $\pm$ 0.43
Placebo challenge	316.66 $\pm$ 8.46	> 2	10.86 $\pm$ 1.11

All results mean $\pm$ s.e.m.

Table 4. Results of kinin pathway

Challenges	Pre-kallikrein (mu/ml)	Kallikrein (mu/ml)	Kallikrein inhibitor (u)	C1 esterase inactivator (mg/dl)
Normal laboratory range	100-200	25-50	> 15	30-140
Dye challenge	220.75 $\pm$ 13	5.58 $\pm$ 1.41	22.16 $\pm$ 1.78	50.83 $\pm$ 5.66
Placebo challenge	200.16 $\pm$ 24	49.50 $\pm$ 10.18	24.60 $\pm$ 3.50	56.60 $\pm$ 10.89

All results mean $\pm$ s.e.m.

The C3 and C4 values were within the normal limits and were not affected by the dye administration. Three out of the sixteen cases had reduced complement activity as measured by CH₅₀.

As shown in Tables 3 and 4, there was activation of the fibrinolytic pathway by the reduction of plasminogen. Fibrinogen and euglobulin were normal before and after the challenges with dye or placebo. The high pre-kallikrein and low kallikrein values showed that the bradykinin system was also activated.

For the bleeding time, differences were recorded between the values obtained before and after the dye intake, but they remained within the normal range.

The four patients challenged for a second time with 10 mg tartrazine had similar clinical and laboratory results as with 50 mg dye.

Discussion

An incidence of overt allergy in the general population of 15-20% is reported (Barkin & McGovern, 1966; Gerrard *et al.*, 1976; Godfrey & Griffiths, 1976; Morrison Smith, 1961; Wilder, 1965), not including carriers and those who show other than the classic symptoms of atopy. There are no exact numbers because of a multiplicity

of factors and reactions, which include a substantial part of the world population (Spector & Farr, 1976).

Our data show that about a third of the allergic population investigated was clinically affected by the yellow dye No. 5, as reported by Stenius & Lemola (1976). It is interesting that the highest incidence of positive responses to tartrazine is found in subjects without the classic personal or familial atopic background.

Three main factors are suggested for this reaction (Bell, 1975; Lockey, 1975): (a) antigen-antibody reactions; (b) food additives; and (c) stress situations. Many of these may start the cascade reactions that activate the Hageman factor, and from these the fibrinolytic system, the kinins system and, indirectly, the complement system. Our data show that the complement system was by-passed in all but three cases. We suggest that an excess of a vasoactive material, such as bradykinin, may induce asthma in a person with hyper-reactive airways or rhinitis (Neuman & Creter, 1977), or other systematic symptoms.

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