

Food anaphylaxis following ingestion of carmine

Etienne Beaudouin, MD*; Gisèle Kanny, MD*; Henri Lambert, MD†; Sophie Fremont, MD‡; and Denise-Anne Moneret-Vautrin, MD*

Background: The risk of sensitization to reactive dyes is well established. The clinical situation is caused most often by synthetic azo dyes and triphenylmethane derivatives but natural dyes such as carmine extracted from dried female insects, *Coccus cacti* (cochineal), have been incriminated.

Objective: Study of a case of anaphylaxis after ingestion of yogurt to establish the responsibility of carmine.

Method: Case report of a patient who received skin prick test and leukocyte histamine release test with carmine and yogurt.

Conclusions: This case provided evidence of an IgE-dependent mechanism and draws attention to the triggering dose of carmine (1 mg) although the acceptable daily intake is up to 5.0 mg per kg of body weight.

INTRODUCTION

Since the first report by Lockey in 1959 describing three cases of urticaria due to tartrazine, the risk of sensitization to reactive dyes has been well established.¹⁻³ This clinical situation is caused most often by synthetic azo dyes and triphenylmethane derivatives but natural dyes such as annatto and carmine have also been implicated.⁴⁻⁶ The pathophysiologic mechanism of these reactions is frequently uncertain because skin tests and laboratory examinations are usually negative.⁶ In a recent paper, however, carmine-specific IgE was demonstrated by positive skin prick tests and radioimmunoassay in three employees who had respiratory symptoms when working in a natural dye factory.⁷ We now describe a patient who had a systemic reaction

following ingestion of carmine and who had an immediate skin test reaction as well as a positive in vitro basophil histamine release test to this substance.

PRESENTATION OF CASE

A 35-year-old female, secretary, was first seen in the Emergency Service of Hôpital Central (CHU de NANCY) with generalized urticaria, angioedema, and asthma that began two hours after she ingested a yogurt containing mixed fruits and the dye carmine (Color Index No. 75470/E120). On admission, her blood pressure was normal. The symptoms and signs of the acute reaction responded promptly to adrenaline.

When seen 6 weeks later in the Allergy Consultation Service, she denied having had any allergic symptoms except for several previous episodes of urticaria and angioedema occurring within hours after eating certain foods, such as delicatessen meats, chocolate, and yogurt with fruits. She noticed that the offending food was always colored red. The amount of carmine that she had ingested in the yogurt was estimated to be 1.3 mg.

Physical examination at this time was normal. Skin prick tests with aeroallergen and food extracts were negative. In contrast, a skin prick test through a drop of the same brand of

yogurt that caused her reaction and another with a powder of carmine resulted in wheals of 3 and 10 mm diameter, respectively (Fig 1), but the white, milky part was negative. The diluent control was negative and the positive control (9% solution of codeine phosphate) resulted in a 3-mm wheal. Skin prick tests with the yogurt and the powder of carmine were negative in two healthy volunteers. The leukocyte histamine release test was carried out according to the method previously published.⁸ The basal histamine release was 5 nM indicating no spontaneous histamine release. The total histamine contained in basophils was 536 nM and the values of histamine release in the presence of carmine ranged from 32 to 130 nM/L. Thus the test was positive, with a maximum of 18% release at a concentration of 0.1 µg carmine/mL (Fig 2).

DISCUSSION

Based on the clinical history and the skin test and leukocyte responses to carmine, we believe that this patient had a true anaphylactic reaction to this dye. Carmine is a natural dye derived from the dried bodies of females of the tropical American insect *Coccus cacti*. This insect, originally from Mexico, lives in the wild on the cochineal figs of the cochineal cactus.⁹ It has been acclimatized to the Spanish Canary Islands, Algeria, and India. The bodies of the females are filled with eggs, and they contain 10% carmine, a powdery substance with a scarlet red color due to its content of carmine acid (MW 492.4 d).^{6,10}

Carmine, reference E 120 in the European Community list of approved colorants, should not be confused with cochineal red A (Color Index No. 16255/E124), a synthetic azo dye that is sometimes called new coccin, ponceau 4R or Food Red 7.⁶ Carmine is

*Service d'Immunologie Clinique et d'Allergologie, Médecine D, CHRU de Nancy, Hôpitaux de Brabois, Rue du Morvan, 54500 Vandœuvre-les-Nancy, France.

†Département d'Urgence et de Réanimation, Service d'Accueil des Urgences au Groupe des Hôpitaux de Ville, Hôpital Central, CHRU de Nancy, 29, Avenue de Lattre de Tassigny, 54035 Nancy Cedex, France.

‡Laboratoire de Biochimie Médicale et Pédiatrique, Faculté de Médecine, Avenue de La Forêt de Haye, BP 184, 54505 Vandœuvre-les-Nancy, France.

Received for publication June 7, 1994.

Accepted for publication in revised form November 3, 1994.



Figure 1. Positive prick skin test with a powder of carmine.

used widely today in the dyeing, printing, and paint industries.⁷ Its use is regulated in the cosmetics, pharmaceutical, and food industries where it is used as a colorant in lipsticks, in the coating of tablets and capsules, and in foodstuffs such as the following:^{6,9}

- candy, ice cream, cookies, pastries
- syrups, liqueurs, vinegar
- cheese, butter, flavored or fermented milk
- delicatessen meats, sausage casing
- bouillon, soup
- jams, caviar, lumpfish eggs

Finally, ingestion of a capsule containing carmine can be used in medical diagnosis to identify an abnormal acceleration of bowel movements. Carmine is nontoxic, a dose of 500 mg/kg/day in man normally being devoid of any adverse effect. By inference, the acceptable daily intake was fixed at 5 mg/kg body weight. Studies carried out in animals have demonstrated no teratogenic effect.¹⁰

There are few published reports of allergic reactions to carmine. Sarkary reported three cases of cheilitis caused by lipstick, with patch tests positive to carmine.¹¹ A number of cases of occupational asthma confirmed by bronchial provocation test have been described in workers in factories where powdered carmine was handled.^{7,9,12}

An unusual observation of a case of extrinsic alveolitis with precipitating serum antibody to carmine was reported in a man working in the food

dye industry.¹³ In some cases of chronic urticaria, carmine has been incriminated on the basis that the symptoms could be reproduced by an oral provocation test.^{5,6} More recently, an English physician described a case of anaphylaxis occurring after application of a cosmetic containing carmine red dye to the skin.¹⁴

In our patient, the fact that the skin prick test and the *in vitro* leukocyte histamine release test with carmine were both positive provides evidence for an IgE-dependant mechanism, confirming the recent findings from Quirce.⁷ The bell-shaped curve is considered very specific for an IgE mechanism. A nonspecific, dose-dependant histamine release can be excluded since 100 mM/L released much less than 0.1 mM/L.

The liberation of histamine and other mediators of anaphylaxis is only possible when there is bridging between the allergen and two specific IgE molecules on the surface of mast

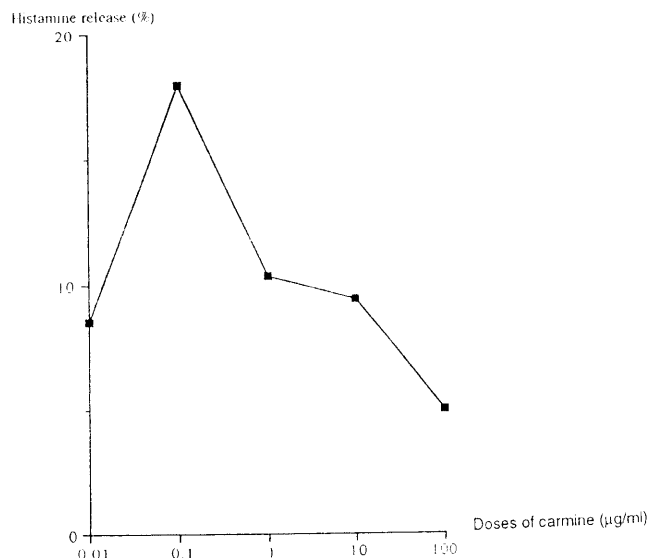


Figure 2. Leukocyte histamine release induced by carmine (E120 dye).

$M^{+} = Ca^{+2},$
 Na^{+}, K^{+}, NH_4^{+}

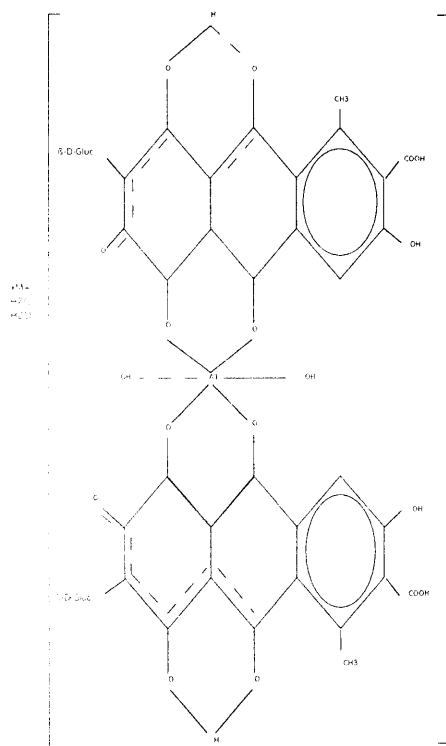


Figure 3. Structural formula of carmine: a hydrated aluminum chelate of carminic acid with an aluminum-carminic acid ratio of 2 (10).

cells and basophils. Carminic acid being a small monovalent hapten, it is possible that bridging could result from two phenomena: one is that the carminic acid in carmine could be bound to residual proteins derived from the bodies of the insects, thereby forming a multivalent conjugate. The presence of protein residues in the commercial dye is assumed.¹⁰ The other is based on the fact that chemical analysis of carmine has shown that the coloring principle is a hydrated aluminum chelate of carminic acid, with an aluminum-carminic acid ratio of 2¹⁰ (Fig 3). In that way, carminic acid

could behave like a divalent compound, allowing it to bridge two specific antibody molecules. The specificity of IgE against carmine could thus be protein (high molecular weight) present in carmine and cochineal or hapten-specific. Quirce argues against the existence of hapten-specific antibodies and says that RAST inhibition data argue for a high molecular 10- to 30-kD antigen present both in cochineal and carmine;⁷ however, the nature of reactogenic antigen remains unknown. Neither skin prick tests nor leukocyte histamine release tests differentiate

hapten-induced from protein-induced IgE-dependant histamine release. Only IgE immunoblot could help resolve the question.

In addition to the fact that the patient we describe is rare, this observation indicates the small amount of carmine that triggered the symptoms: 1 mg. This dose is very far from the admissible daily ingestion, up to 5.0 mg per kg of body weight. It is also very different from the dose of 100 mg, which was used for oral challenge in a patient sensitized by carmine inhalation and having rhinitis and asthma.⁷ This case draws attention to the need of knowing the amount of the hidden allergens in food before performing oral challenges.

ACKNOWLEDGMENTS

Our thanks to Professor D.A. Levy for the skilled translation and revision of the manuscript.

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Requests for reprints should be addressed to:
Etienne Boudouin, MD
Service d'Immunologie Clinique et
d'Allergologie, Médecine D'Urgence, Hôpital
VAUTRIN
1 Hôpital Central
Av. de l'Industrie de Toulon
54000 Nancy, France

INCREASED PREVALENCE OF ASTHMA AND WHEEZING AMONG INNER-CITY CHILDREN

In order to estimate prevalence of asthma and wheezing among inner-city children the authors completed a random digit dialing telephone survey of 662 households (with 1285 children less than 18 years of age) in Bronx County, New York in 1991.

The cumulative prevalence of asthma among the children was 14.3%, and 8.6% had had asthma within the previous 12 months, compared with 4.3% who had had asthma within the previous 12 months in the nationwide Health Interview Survey of 1988. Wheezing within the previous 12 months (period prevalence) was also reported for an additional 4.2% of the Bronx children. Cumulative prevalence of asthma was significantly higher among Hispanic children (17.9%) compared with blacks (11.6%), whites (8.2%), and others (10.4%). Among Hispanic children both cumulative prevalence and period prevalence of asthma were significantly higher for those with annual household incomes less than \$15,000. The period prevalence of "wheeze" without a diagnosis of asthma was slightly higher among whites (6.4%) and blacks (5.8%) than Hispanics (2.9%) ($P < .1$); period prevalence for the combination of wheeze only and asthma was similar for whites (14%) blacks (12.7%) and Hispanics (12.9%). Of the children reported to have asthma who had wheezed during the previous year, 89.5% had had one to three episodes and 10.5% had had four to 12 episodes within the previous year, 9.2% reported disturbance of sleep by wheezing an average of more than two nights per week; similar proportions of those reporting wheezing only without a diagnosis of asthma had had four episodes within the previous year and nocturnal wheezing more than two nights per week.

These observations suggest prevalence of asthma among inner-city children may be much higher than for other children in the United States.

—RMS

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