

Popsicle-induced anaphylaxis due to carmine dye allergy

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Background: IgE-mediated hypersensitivity is a suggested mechanism to explain adverse reactions from carmine-containing products.

Objective: To describe a patient who experienced anaphylaxis after ingestion of a popsicle colored with carmine and to provide additional evidence that the adverse reaction was IgE-mediated.

Methods: The patient and her husband underwent skin prick tests to the popsicle and carmine. The patient also received skin prick tests and/or open oral challenge to each of the other components of the incriminated food. Topical application of cosmetics with and without carmine to the patient's forearm was also performed. To confirm carmine-specific IgE, a Prausnitz-Kustner (P-K) test was performed using the patient's husband as recipient. Twenty control subjects also were tested to carmine by skin prick test.

Results: The patient showed 4+ skin prick test responses to the popsicle and carmine. Skin prick tests and/or open oral challenge to each of the other components of the popsicle were negative. The patient's husband's and 20 control subjects' skin prick tests to carmine were negative as was the patient's husband's skin prick test to the popsicle. Skin prick test reactivity to the popsicle and carmine were successfully transferred to the patient's husband in P-K format. Cosmetics applied to the patient's forearm elicited no immediate response.

Conclusion: The positive skin prick tests to the popsicle and carmine and the successful (P-K) transfer of skin prick test reactivity support a carmine-specific, IgE-mediated mechanism in explaining our patient's popsicle-induced anaphylaxis.

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INTRODUCTION

IgE-mediated responses to food colorants are rarely reported.^{1,2} Carmine, a biogenic dye added to foods, cosmetics and drugs has been implicated in occupational asthma,³⁻⁶ extrinsic allergic alveolitis,^{7,8} cheilitis,^{9,10} gastrointestinal complaints,⁴ urticaria/angioedema, asthma,¹¹ and anaphylactic shock.^{10,12} Positive responses to carmine by skin prick tests, inhalational and oral challenges, basophil histamine release, and RAST also have suggested that an IgE-mediated mechanism may be responsible for these events.³⁻¹²

We describe a patient with anaphylaxis after ingestion of a popsicle col-

ored with carmine, who also exhibited immediate skin prick test reaction to the popsicle and carmine despite no response to other components of the popsicle on either skin prick tests or open oral challenge. Our confirmation of carmine-specific IgE by Prausnitz-Kustner (P-K) test has not been reported previously.

CASE REPORT

The patient is a 27-year-old woman with anaphylaxis requiring emergency treatment following ingestion of a Good Humor SnoFruit popsicle colored with carmine. She experienced nausea within minutes and pruritus, urticaria, and hypotension with tachycardia (blood pressure = 70/palpable, pulse = 134) within three hours of ingesting this food item. The patient's distress responded to intravenous fluids, epinephrine, and diphenhydramine

and she was discharged improved on loratidine 18 hours after presentation. She has avoided carmine-containing products and, at 2-year followup, she has not had recurrence of anaphylaxis.

Her past medical history is significant for allergic rhinitis and positive skin prick tests to aeroallergens (pollens, animal allergens, and molds). The patient also recalled an immediate, pruritic, erythematous eruption after applying a blush, colored with carmine (Clinique), directly to facial skin, but not when the blush was used over foundation makeup. She had no other significant past medical or family history and was taking no medications.

METHODS

Liquid carmine; containing "not less than 3.5% carminic acid," water, potassium hydroxide, ammonium hydroxide, and glycerine; was obtained from the Good Humor company's supplier and was used undiluted for skin prick tests. Histamine base (1 mg/mL) positive control was obtained from Center Laboratories (Port Washington, NY) and negative control (50% vol/vol glycerine) was supplied by Miles Inc (Elkhart, IN). Skin prick tests were graded using a standard 0 to 4+ rating system employed at our institution.

The patient and her husband underwent skin prick tests to the popsicle and carmine several weeks after the initial anaphylactic episode. Skin prick tests and/or open oral challenge to each of the other available components of the food individually or within other processed foods, were also performed on the patient.

To confirm the presence of carmine-specific IgE, a Prausnitz-Kustner (P-K) test was performed using the patient's husband as a recipient. After obtaining informed consent, the patient's serum was injected intrader-

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Figure 1. Results of patient's skin prick tests to popsicle ingredients and foundation and blush samples. C1, C2, carmine samples; H, histamine; S, saline; FP, fruit popsicle; AJ, apple juice from concentrate; BL, blush; F1,F2,F3, foundation samples; and GJ, grapefruit juice containing carmine.

mally into several sites on her husband's arms. The right arm was injected with heat-treated (55 °C × 30 minutes) serum and the left arm was injected with unheated serum. Skin prick tests with the popsicle and carmine were repeated at these sites 63 hours later.

Twenty control subjects also underwent skin prick testing to carmine. Three non-carmine containing foundation samples and one carmine containing blush sample were applied to the patient's forearm in an effort to reproduce the patient's historically noted, facial skin responses.

RESULTS

The patient had 4+ (erythema and wheal with pseudopod formation) skin prick test responses to the popsicle and carmine (Fig 1). Skin prick tests and/or open oral challenge to each of the other components of the popsicle were negative (Table 1). Histamine control was 3+ and negative control was nonreactive in all cases. The patient's husband's and 20 control subjects' skin prick tests to carmine were negative as was the spouse's skin prick test to the popsicle.

Skin prick tests with the popsicle and carmine repeated at the serum-injected sites 63 hours later (P-K test) were 2+ (erythema of 22 mm and wheal of 3 mm) and 4+ (erythema and wheal with pseudopod formation) respectively on the husband's left arm and negative on his right (heated serum sites) as shown in Figure 2.

Neither the immediate pruritic erythematous eruption described nor any

other change followed the application of carmine-containing cosmetic samples to the patient's forearm (Fig 1).

DISCUSSION

Carmine and cochineal are natural red dyes, derived from the dried bodies of female cochineal insects *Dactylopius coccus* Costa (*Coccus cacti* L), a parasite of the prickly pear cactus (*Nopalea coccinellifera*). The insect and cactus are native to Mexico where Cortez found the Aztecs using cochineal to color their food, clothing, and bodies. The subsequent discovery that this dye was 10 times stronger than kermes, the (also insect-derived) red dye used in Europe at the time, made it an important article of commerce. The cochineal trade declined with the introduction of synthetic colors in 1856.^{13,14} In the 1990s, preference for foods without synthetic ingredients has led to resurgent use of natural colors. This, together with the strength and stability of carmine, determines its wide use in prepared foods.

Currently, large plantations of cactus are devoted to cochineal extract production in the Canary Islands and Peru which are leading producers. At sexual maturity (approximately 100 days old), the female insect bodies are filled with eggs which contain the greatest concentration of carmine. Just

Table 1. Results of Skin Prick Tests and/or Open Oral Challenge to Popsicle Ingredients

SnoFruit Popsicle Ingredients	Skin Prick Test	Open Oral Challenge
Water	ND*	Negative
Pineapple	ND	Negative
Sugar	ND	Negative
Apple juice from concentrate	Negative	Negative
White grape juice from concentrate	ND	Negative
Corn syrup solids	ND	Negative
Pineapple juice from concentrate	ND	Negative
Natural flavors	NA†	NA
Citric acid	ND	Negative
Annatto	Negative	Negative
Carmine	Positive	ND
Guar gum	ND	Negative
Locust bean gum	ND	Negative
Carrageenan gum	ND	Negative
Xanthan gum	ND	Negative

* ND = not done.

† NA = not available (manufacturer's trade secret).

before egg laying, the insects are brushed off the cactus by hand, collected, and dried.

Carmine (color index no. 75470) and cochineal extract share the same European Economic Community (EEC) number, E120. The coloring principle of both is believed to be carminic acid, $C_{22}H_{20}O_{13}$, (MW 492.39), sometimes termed "Natural Red #4." Cochineal extract is the concentrated solution remaining after alcohol is removed from an aqueous-alcohol extract of cochineal insects. Carmine is the aluminum or calcium-aluminum lake on an aluminum hydroxide substrate of carminic acid. Several studies exploring the safety of carmine in rats suggest no genotoxic, teratogenic, or carcinogenic properties.¹⁵⁻¹⁷ US Food and Drug Administration specifications state that cochineal extract should contain not more than 2.2% protein ($N \times 6.25$). Although no corresponding guidelines for carmine exist, protein levels are likely to be considerably higher because carmine is a more concentrated material. For example, cochineal contains 1.8% carminic acid while carmine contains 50% carminic acid, though both are generally sold in water soluble forms diluted to contain 2.2% to 3.5% carminic acid.^{14,18}

Neither carmine nor cochineal extract are Food and Drug Administration certifiable (synthetic) color additives. Foods, cosmetics, and drugs containing these colorants (or any other US Food and Drug Administration approved dye exempt from certification) need not bear labels specifying these ingredients. According to 21 Code of Federal Regulations, Sec 101,¹⁸ these agents may be acknowledged simply as: "color added," "artificial color," or "artificial color added." Alternatively, such components may be declared as "colored with _____" or "_____color," with the name of the color additive supplied. Furthermore, in our experience, the coloring of foods and cosmetics is often a highly protected trade secret of manufacturers, making confirmation of carmine in foods and cosmetics often remarkably difficult. Table 2 is,

therefore, only a partial list of foods, cosmetics, and drugs that may (and often do) contain carmine.

Three previously described cases of anaphylaxis associated with carmine are notable. The first, reportedly, was due to contact with a carmine-containing make-up stick used on a military recruit for casualty simulation.¹² Unfortunately, no correlative studies (eg, skin prick tests, RAST or other) were performed. Kagi et al reported a pa-

tient who experienced anaphylaxis after Campari-Orange ingestion who had positive skin prick test to carmine. This patient was found initially to have a negative carmine RAST; however, after a year "during which the patient repeatedly suffered minor allergic episodes due to undeclared red-dyed food," a class 2 positive RAST (0 to 8 Pharmacia RAST units) was demonstrated.¹⁰ Most recently, Beaudouin et al reported a patient with urticaria, an-



Figure 2. Results of P-K test on patient's husband. Left arm, unheated serum; right arm, heated serum. H, histamine; S, saline; C, carmine; FP, fruit popsicle; GJ, grapefruit juice.

Table 2. Potential Carmine-Containing Foods, Cosmetics, and Drugs

Foods	Cosmetics	Drugs
Candy	Blushes	Vitamins (chewable)
Ice cream/popsicles	Lipsticks	Homeopathic medications
Juice drinks	Eyeshadows	
Fruit fillings (eg, in baked goods)		
Strawberry milks		
Port wine cheese		
Artificial crab/lobster products		
Cherries in fruit cocktails		
Yogurts		
Syrups		
Liqueurs		
Vinegar		
Puddings		
Lumpfish eggs, caviar		
Processed meats*		

* Note: carmine cannot legally be added to meat products in the USA.

gioedema, and asthma two hours after ingestion of a yogurt colored with carmine. This patient had positive skin prick tests to carmine and to the red portion (but not the white portion) of the yogurt as well as a positive leukocyte histamine release test.¹¹

In the present case, positive skin prick tests to both the popsicle and carmine and negative open oral challenge and/or skin prick tests to the other available popsicle ingredients along with the successful transfer of skin prick test reactivity to the patient's husband by P-K test approach support a carmine-specific, IgE-mediated mechanism for our patient's anaphylaxis. This is the first carmine-induced anaphylaxis with IgE-based sensitivity demonstrated by P-K test. This approach was chosen because immunosorbent assays (eg, RAST) are difficult to interpret, especially without known positive and negative control sera; leukocyte histamine release data may be similarly flawed. Carmine has been shown to have both high and low molecular weight components either of which theoretically may cause sensitization.¹⁹ Characterization of these and assessment of IgE specificity are being pursued actively in our laboratory.

One might question whether our patient also was sensitive to other popsicle components and that the quantities of these, used for skin prick tests and/or open oral challenge, were insuf-

ficient to elicit a response. In fact, the actual amounts of each ingredient in the popsicle are unavailable as manufacturer's trade secrets. While an additional offender cannot be ruled out conclusively by the testing reported, our patient has continued to freely consume *all* available components of the popsicle (other than carmine) in her day-to-day diet for the past 2 years without difficulty. In any event, such marginal concerns cannot lessen the significance of the patient's carmine-specific IgE as demonstrated by skin prick tests and P-K approach.

Exposure to carmine potentially may occur at any step from production and processing to ingestion or other use by consumers. Inhalational and oral routes of initial sensitization are well established for atopic allergens. Topical application of allergen to skin is less commonly cited as a means of eliciting an IgE response. Notably, our patient's only known previous carmine exposure was to Clinique blush which caused an immediate, pruritic, erythematous eruption when used directly on facial skin, but not when applied over a foundation or directly to non-facial skin areas such as her forearm. Since ingestant exposures cannot be excluded, it remains unclear when and by which route sensitization to carmine occurred; nonetheless, it is intriguing to speculate that topical application may have been critical. As the sensi-

tizing component(s) of carmine remain(s) undefined, possible contributions of additional and/or cross-reactive allergen exposures also are unknown.

We were fortunate in having "carmine for color" listed on the packaging of the Good Humor Snofruit popsicle that our patient ingested prompting us to consider it as a potential offender; however, as noted above, carmine need not be specified by name. It is important to educate patients, sensitive to carmine, to beware of the diverse foods, drugs, and cosmetics that are potentially colored with carmine. Despite the general public's belief that lack of synthetic ingredients is synonymous with "healthful," our patient's anaphylaxis was potentially life threatening—a dramatic denial of this concept.

Finally, we are aware of the view among healthcare professionals that food color additive allergic reactions are rare, if they occur at all. With this report, and those cited above, we urge fellow clinicians to be aware of possible carmine-induced allergic reactions in patients who present with otherwise unexplained cutaneous or systemic events after suggestive exposures.

ADDENDUM

The authors have identified two additional patients with positive skin prick tests to carmine and anaphylaxis following the ingestion of carmine-containing foods in the time since this manuscript was accepted for publication.

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