

Anaphylaxis to carrageenan: A pseudo-latex allergy

Susan M. Tarlo, MBBS,^a Jerry Dolovich, MD,^b and
Charles Listgarten, MD^c Toronto and Hamilton, Ontario, Canada

Background: Anaphylactic reactions during a barium enema have been attributed to allergy to latex on the barium enema device. The observation of anaphylaxis during barium enema without latex exposure or latex allergy led to the performance of an allergy skin test to the barium enema solution.

Methods: Individual components of the barium enema solution were obtained for double-blind skin testing. A RAST to identify specific IgE antibodies to the skin test active agent was established.

Results: Carrageenan, a component of the barium enema solution, produced positive reactions to allergy skin test and RAST. Gastrointestinal symptoms for which the patient was being investigated by the barium enema subsequently disappeared with a diet free of carrageenan.

Conclusions: Carrageenan is a previously unreported cause of anaphylaxis during barium enema. It is an allergen widely distributed in common foods and potentially could account for some symptoms related to milk products or baby formula. (*J ALLERGY CLIN IMMUNOL* 1995; 95:933-6.)

Key words: Anaphylaxis, food allergy, carrageenan, barium enema reaction

Carrageenans are commonly ingested in milk and pharmaceutical products. Although they are known to have several immunologic effects in animals, to our knowledge IgE-dependent reactions have not been reported. We describe a patient who during a barium enema had anaphylaxis apparently caused by latex allergy. Subsequently it was found that the anaphylaxis was due to carrageenan in the barium enema solution, and her previous gastrointestinal symptoms could be attributed to carrageenans ingested with milk products and with other foods.

CASE REPORT

A 26-year-old woman underwent a barium enema for an 8-month history of daily nausea, vomiting, abdominal bloating, and diarrhea attributed to irritable bowel syn-

drome. Within minutes of receiving the enema she had abdominal cramps and mild generalized pruritus, which progressed to generalized urticaria, hypotension, transient loss of consciousness, chest tightness, wheezing, and cyanosis. She was treated in the hospital for anaphylaxis and recovered within a few hours, and she was discharged home the next day. She had a history 2 years earlier of allergic rhinitis, asthma, and urticaria related to cat exposure, which she was subsequently able to avoid. She continued to have mild asthma symptoms with cold air and exercise but did not require regular medication for this. She had previously worn latex gloves intermittently and noted local pruritus but no rash or other symptoms with latex exposure. A barium meal examination 6 months previously was associated with nausea but no other symptoms. One month after the anaphylaxis, physical examination was normal. Reaction to skin prick test was positive to cat (10 mm mean wheal diameter) and to the positive control, 1 mg/ml histamine (4 mm mean wheal diameter), but negative to a skin test solution consisting of ammoniated raw latex (Bencard, Mississauga, Ontario, Canada).

Latex-induced anaphylaxis was suspected from the patient's history, but it was subsequently learned that the barium enema delivery system contained no latex. Result of a skin prick test with the barium enema solution of the type used for her study (Liquid Polibar, Therapex division of E-Z-EM Canada Inc.) was positive (10 mm mean wheal diameter with surrounding

From ^aThe Toronto Hospital, Western Division, Toronto, ^bMcMaster University Medical Centre, Hamilton, and ^cNorthwestern Hospital, Toronto.

Received for publication May 4, 1994; revised July 7, 1994, accepted for publication Aug. 23, 1994.

Reprint requests: S. Tarlo, MBBS, The Toronto Hospital Western Division, EC4-008, 399 Bathurst St., Toronto, Ontario M5T 2S8, Canada.

Copyright © 1995 by Mosby-Year Book, Inc.

0091-6749/95 \$3.00 + 0 1/1/60292

TABLE I. Principal products containing carrageenans

Dairy products: Chocolate milk, thickened and sterilized cream, milk desserts, products made from fresh cheese
Sorbets and ice creams
Products with gelling agents: Candied fruits, icing sugar, jams, jellies
Powdered products: Powdered milk desserts, hot milk pudding, instant drinks, confectioner's custard icing
Low-calorie and reconstituted products: Simulated chocolate milk, coffee whiteners, reconstituted diet products, formulated baby milks
Seasonings, sauces, soups: Emulsified sauces (salad dressings, mayonnaise), gravies and soups
Cured meat: Glazed ham, pâtés, flavored jellies, canned meat, convenience and frozen foods, pet food
Pharmaceuticals: Gastric packings, barium contrast medium, toothpastes and tooth powders

Product information from Sanofi Bio-Industries, Mississauga, Ontario, Canada, lists substances that may contain carrageenans.

flare) in the patient and negative in two control subjects.

The manufacturer, Therapex, provided individual components of the barium enema solution in coded form, labeled 1 to 13 in separate bottles. The amount provided was such that the addition of 100 ml water to each bottle yielded the concentration present in Liquid Polibar solution. Skin prick tests were performed on the patient with these 13 solutions; there was a positive reaction (8 mm mean wheal diameter with surrounding flare) with one constituent, subsequently identified as 0.4% wt/vol sodium carrageenan (Sanofi Bio-Industries, Mississauga, Ontario, Canada). Results of skin prick tests with this solution in three control subjects were negative. A skin test result with a commercial skin test preparation of carrageenan gum (1:50 wt/vol, Miles Inc., Canada) was borderline (2 mm mean wheal response).

The sodium carrageenan obtained from Sanofi Bio-Industries was also used to test for serum IgE antibodies.¹ Cyanogen bromide-activated disks were incubated with 100 mg/ml carrageenan and used in a RAST. Binding of iodine 125-labeled anti-IgE (Kabi Pharmacia Canada Inc., Baie d'Urfe, Quebec, Canada) was 10.5% with the patient's serum; 3.5% and 2.8% with two control sera with high IgE concentration; and 2.6%, 3.2%, and 2.2% with normal control sera. We concluded that the patient's serum contained IgE antibodies to carrageenan.

The patient additionally reported that her gastrointestinal symptoms were worse after the ingestion of certain milk products such as some ice cream, yogurt, and chocolate milk products, but she had no symptoms from plain milk. On the basis of the skin test result she was advised to exclude carrageenan-containing products from her diet. During the 5 months since that time she has had no gastrointestinal symptoms except after occasional inadvertent ingestion of such products.

DISCUSSION

Carrageenans are gelatinous substances first used more than 600 years ago by residents of County Carraghen in Ireland. They were obtained

from carrageen (*Chondrus crispus*), also called Irish moss,² and later also from other species of red marine algae. They were used for their ability to cause milk to gel, which the French adopted to make blancmange. *C. crispus* is a small tufted seaweed that grows along the rocky parts of the Atlantic coast of the British Isles, Europe, and North America. Other species are found off the coasts of South America, North Africa, Indonesia, and the Philippines.

Carrageenan is used for curing leather and as an emulsifying and suspending agent in pharmaceuticals, certain food products, cosmetics, and shoe polishes. The food industry uses carrageenan as a clarifying agent in some beverages, as a suspending agent, and as an additive to control crystal growth. It therefore can be found in some ice creams, cream, chocolate milk, some yogurts, frozen treats, salad dressings, and barbecue sauces (Table I).

Carrageenans are sulfated polygalactans. There are several types, which vary in total sulfate content and in molecular configuration.³ Different types can come from the same or different species of algae. They have been shown to be immunogenic,⁴ and antisera raised in goats to α -carrageenan have distinct specificity from antibodies to κ - and ι -carrageenans, which crossreact.⁵ The company supplying carrageenan for manufacture of the barium solution in this patient uses blends of 10 different types of carrageenans, some of which are mainly κ -carrageenan whereas others, particularly those used in milk products, contain mainly ι -carrageenan.

Animal studies have shown several different immunologic effects of carrageenan. Delayed hypersensitivity has been demonstrated in guinea pigs to a carrageenan preparation that contained about 1.5% polypeptides⁶ and has also been shown in mice.⁷ In addition, an adjuvant effect of carrageenan has been reported in guinea pigs in induc-

ing delayed hypersensitivity.⁸ Carrageenans have also been used to induce experimental acute inflammation in rat footpad models⁹ and in rat joints, possibly via substance P.¹⁰

Gastrointestinal effects of carrageenan in animals have also been reported, particularly colonic or cecal ulceration with some forms of carrageenan in guinea pigs,¹¹ rabbits,¹² and monkeys.¹³ Toxic effects on macrophages have been implicated as a factor in this response in guinea pigs and monkeys.^{11, 14} However, no effect on macrophages from mice was found in vitro with the use of autoclaved carrageenan.¹⁵ The relevance of these findings to human beings remains speculative, and although concern has been raised of the possibility of similar effects in human beings,¹⁶⁻¹⁸ to date this has not been demonstrated. In particular, IgE-dependent anaphylaxis to carrageenan has not been reported previously to our knowledge, although another polysaccharide hydrocolloid, pectin, has been reported to induce occupational asthma on the basis of immediate hypersensitivity.¹⁹

In our patient we can conclude that the anaphylaxis during a barium enema was due to allergy to carrageenan. Latex proteins have been identified as a cause of many episodes during barium enema procedures of anaphylaxis induced by the latex in the barium enema device.^{20, 21} It has been suggested that earlier reports of unexplained anaphylaxis during barium enema were also due to unrecognized latex allergy.²² However, in our patient no latex was in the tip of the barium enema device and results of skin tests to latex were negative. The reported case illustrates that components of the barium enema solution, particularly carrageenan, should therefore be suspected as a possible cause of anaphylaxis during barium enema.

The role of carrageenans in the gastrointestinal symptoms of this patient is also of interest. Oral challenges with carrageenan were not performed because of her history of anaphylaxis. Even though she had no urticaria or respiratory symptoms associated with the gastrointestinal symptoms, these symptoms could be due to allergy to carrageenan. It is known that double-blind allergen ingestion challenges in people with food allergy can elicit exclusively gastrointestinal symptoms.²³ A direct inflammatory effect comparable to that observed in animals is also possible but speculative. Further consideration of the possible direct or immunologic effects of carrageenan in the pathogenesis of irritable bowel syndromes or inflammatory bowel syndromes may be warranted, particularly in patients with symptoms exacerbated by milk prod-

ucts, including infant formulas, in the absence of milk allergy or lactose intolerance.

We acknowledge the technical support of Susan Evans, who performed the RAST, and the secretarial support of Kerry Cheung.

REFERENCES

1. Ceska M, Eriksson R, Varga JM. Radioimmunosorbent assay of allergens. *J ALLERGY CLIN IMMUNOL* 1972;49:1-9.
2. Irish moss. In: The new Encyclopaedia Britannica, micro-paedia; vol 6. 15th ed. Chicago: Encyclopedia Britannica, Inc, 1993:385.
3. Lawson CJ, Rees DA, Stancioff DJ, Stanley NF. Carrageenans. Part VIII. Repeating structures of galactan sulphates from *Furcellaria fastigiata*, *Gigartina canaliculata*, *Gigartina chamissoi*, *Gigartina atropurpurea*, *Ahnfeltia durvillaei*, *Gymnogongrus furcellatus*, *Eucheuma cottonii*, *Eucheuma spinosum*, *Eucheuma isiforme*, *Eucheuma uncinatum*, *Aghardhiella tenera*, *Pachymenia hymantophora*, and *Gloiopeltis cervicornis*. *J Chem Soc* 1973;2177-82.
4. Johnston KH, McCandless EL. The immunological response of rabbits to carrageenans, sulfated galactans extracted from marine algae. *J Immunol* 1968;101:556-62.
5. Dininno V, McCandless EL. Anti-carrageenans. *Immunochimistry* 1978;15:273-4.
6. Mizushima Y, Noda M. Induction of delayed hypersensitivity by carrageenan. *Experimentia* 1973;29:605-6.
7. Yoshino S, Ohuchi K, Tsurufuji S. Induction of a delayed type hypersensitivity to carrageenin in mice. *J Pharmacobiodyn* 1982;5:266-72.
8. Mizushima Y, Murata J, Horiuchi Y. Use of carrageenan as an adjuvant of delayed hypersensitivity. *Int Arch Allergy* 1974;47:532-6.
9. Popper H, Picher O, Auer H. Reduction of carrageenan-bradykinin and histamine-induced acute inflammation by experimental eosinophilia in rats. *Immunology* 1982;46:589-94.
10. Lam FY, Ferrell WR. Inhibition of carrageenan induced inflammation in the rat knee joint by substance P antagonist. *Ann Rheum Dis* 1989;48:928-32.
11. Abraham R, Fabian RJ, Goldberg L, Coulston F. Role of lysosomes in carrageenan-induced cecal ulceration. *Gastroenterology* 1974;67:1169-81.
12. Watt J, Marcus R. Experimental ulcerative disease of the colon in animals. *Gut* 1973;14:506-10.
13. Benitz KF, Goldberg L, Coulston F. Intestinal effects of carrageenans in the rhesus monkey (*Macaca mulatta*). *Food Cosmet Toxicol* 1973;11:565-75.
14. Mankes R, Abraham R. Lysosomal dysfunction in colonic submucosal macrophages of rhesus monkeys caused by degraded iota carrageenan. *Proc Soc Exp Biol Med* 1975;150:166-70.
15. Simon L, Jones TL. Re-evaluation of carrageenan cytotoxicity for macrophages. *J Reticuloendothelial Soc* 1979;25:133-8.
16. Fleiss PM, Gordon J, Douglas JM. One more hazard [Letter]. *West J Med* 1980;132:4.
17. Marcus R, Watt J. Potential hazards of carrageenan [Letter]. *Lancet* 1980;1:602-3.
18. Marcus R, Watt J. Danger of carrageenan in foods and slimming recipes [Letter]. *Lancet* 1981;1:338.

19. Cohen A, Forse M, Tarlo SM. Occupational asthma caused by pectin during the manufacture of jam. *Chest* 1993;103:309-11.
20. Sussman G, Tarlo SM, Dolovich J. The spectrum of IgE mediated responses to latex. *JAMA* 1991;265:2844-7.
21. Ownby DR, Tomlanovich M, Sammons N, McCullough J. Anaphylaxis associated with latex allergy during barium enema examinations. *AJR AM J Roentgenol* 1991;156:903-8.
22. Warpenski JR, Bush RK. Latex hypersensitivity. *Am J Med* 1991;90:769-70.
23. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J ALLERGY CLIN IMMUNOL* 1976;58:500-15.

Bound volumes available to subscribers

Bound volumes of the THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY are available to subscribers (only) for the 1995 issues from the Publisher, at a cost of \$73.00 for domestic, \$99.51 for Canadian, and \$93.00 for international subscribers for Vol. 95 (January-June) and Vol. 96 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone 1 (800) 453-4351 or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.