

Brief Report

ANAPHYLAXIS FROM THE CARBOXYMETHYLCELLULOSE COMPONENT OF BARIUM SULFATE SUSPENSION

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ALTHOUGH allergic reactions to barium sulfate suspensions are estimated to occur at a rate of less than 2 per million,^{1,2} the frequency has been reported to be increasing.^{3,4} The cause of these reactions is not known,⁵⁻⁹ but the additives in barium suspensions,¹⁰⁻¹³ medications such as glucagon,³ and exposure to latex¹⁴⁻¹⁷ — for example, through contact with rubber gloves or balloons — have all been implicated.

We describe a patient with anaphylaxis induced by the carboxymethylcellulose sodium in barium sulfate suspension. The reaction occurred after an upper gastrointestinal examination.

CASE REPORT

A 63-year-old woman was admitted to the hospital in May 1994 because of an anaphylactic reaction after a double-contrast upper gastrointestinal examination. Before the examination, she had no abdominal discomfort. She had no history of atopic dermatitis, allergic rhinitis, or asthma and had not had any side effects from earlier barium studies. The examination was performed with a 100 percent (wt/vol) suspension of barium sulfate (Balgin S Solution number 3, Kaigen, Osaka, Japan) and gas-producing granules (Kaigen). No other medications were given. The examination revealed no gastritis or peptic ulcers. About 30 minutes later, the patient reported generalized pruritus and urticarial lesions on her abdomen, arms, and face, as well as mild periorbital edema. Within minutes she lost consciousness briefly and had tonic convulsions.

On admission, a complete blood count, blood chemical values, and serologic tests were normal. Chest radiographs revealed no abnormalities. The white-cell count was 6400 per cubic millimeter, with 0.5 percent eosinophils. The patient again had transient loss of consciousness and hypotension. She was resuscitated with

subcutaneous injections of epinephrine (0.5 mg), intravenous infusion of fluids, and two injections of methylprednisolone sodium succinate (250 mg each). The urticarial lesions disappeared after 24 hours. The patient recovered fully and went home eight days later.

METHODS

Skin Testing

After obtaining oral informed consent, we studied the patient and three healthy subjects without atopy or allergies. We conducted skin-scratch tests for each of the components of the barium suspension: barium sulfate, carboxymethylcellulose sodium, sodium metaphosphate, sodium benzoate, sodium dehydroacetate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, glacial acetic acid, saccharin sodium, and flavorings. All substances (purity, more than 98.0 percent) were mixed with petrolatum and liquid paraffin (10 percent wt/wt) and applied to the skin. The response was evaluated 20 minutes later. The patient also underwent skin-scratch testing with barium sulfate suspension that contained 1.2 percent carboxymethylcellulose sodium and with barium suspension free of carboxymethylcellulose. All the components of the suspension as well as the suspension that did not contain carboxymethylcellulose sodium were obtained from Kaigen.

Histamine Release from Isolated Leukocytes

Peripheral blood was withdrawn from the forearm vein of the patient and the three subjects. The blood was layered in a solution containing 4.5 percent Ficoll and 12 percent iohalamate meglumine (specific gravity, 1.077) and centrifuged at 350×g for 35 minutes to isolate the leukocytes. Isolated leukocytes were washed twice with Hanks' balanced salt solution, resuspended in the same buffer, and then placed in eppendorf tubes in aliquots of 180 μl.

The leukocyte suspension was incubated for five minutes at 37°C before the diluted carboxymethylcellulose sodium with the suspending buffer was added (final volume, 200 μl). The reaction was stopped after 15 minutes. To examine the effect of *N*-formyl-methionyl-leucyl-phenylalanine,¹⁸ it was added to the leukocyte suspension instead of carboxymethylcellulose. The reaction was stopped by cooling the mixture on ice, and each tube was then centrifuged at 1800×g for five minutes at 4°C. Both the supernatant and the precipitate were assayed for histamine content according to a method described previously,¹⁹ and the results were presented as a percentage of histamine release.

RESULTS

The results of skin testing are summarized in Table 1. A positive reaction was observed only with carboxymethylcellulose sodium (wheal, 21 by 21 mm in diameter; flare, 55 by 45 mm) and with the barium sulfate suspension containing carboxymethylcellulose sodium (wheal, 25 by 20 mm; flare, 57 by 50 mm). The results of skin testing with the gas-producing granules — sodium bicarbonate, tartrate, and saccharin sodium — were also negative. The three control subjects had no response to all agents tested.

The degree of histamine release from leukocytes that was induced by carboxymethylcellulose sodium was studied in vitro (Fig. 1A). The patient's leukocytes responded to carboxymethylcellulose sodium at concentrations ranging from 10^{-4.5} to 10^{-2.6} percent, with a maximal response at a concentration of 10^{-3.6} percent. The dose-response curve for the ef-

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TABLE 1. RESULTS OF SKIN TESTING IN THE PATIENT.*

SUBSTANCE TESTED	WHEEL	FLARE
	mm	
Barium sulfate	—	—
Carboxymethylcellulose sodium	21×21	55×45
Sodium metaphosphate	—	—
Sodium benzoate	—	—
Sodium dehydroacetate	—	—
Ethyl parahydroxybenzoate	—	—
Propyl parahydroxybenzoate	—	—
Glacial acetic acid	—	—
Saccharin sodium	—	—
Flavoring	—	—
Barium sulfate suspension containing 1.2% carboxymethylcellulose sodium	25×20	57×50
Barium sulfate suspension without carboxymethylcellulose sodium	—	—

*The reaction was assessed after 20 minutes. Results were considered positive if the diameter of the wheal was 5 mm or more. Three control subjects had negative reactions to all tested substances.

fect of carboxymethylcellulose sodium on histamine release was bell-shaped. There was no release of histamine from leukocytes from the three normal subjects, even in the presence of high concentrations of carboxymethylcellulose sodium. The degree of histamine release by basophils in response to *N*-formyl-methionyl-leucyl-phenylalanine was similar in the patient and the three normal subjects (Fig. 1B), indicating that all had normal signal transduction with respect to histamine secretion.

DISCUSSION

Although the carboxymethylcellulose component used for the barium study, skin testing, and histamine-release experiment contained chloride, sulfate, and silicate as impurities (less than 0.64 percent, 0.96 percent, and 0.5 percent, respectively), it is quite unlikely that the inorganic salts caused the anaphylactic response. Therefore, the results of skin testing and in vitro histamine release as a whole indicated that carboxymethylcellulose sodium was the antigen responsible for the anaphylactic response to barium suspension in our patient.

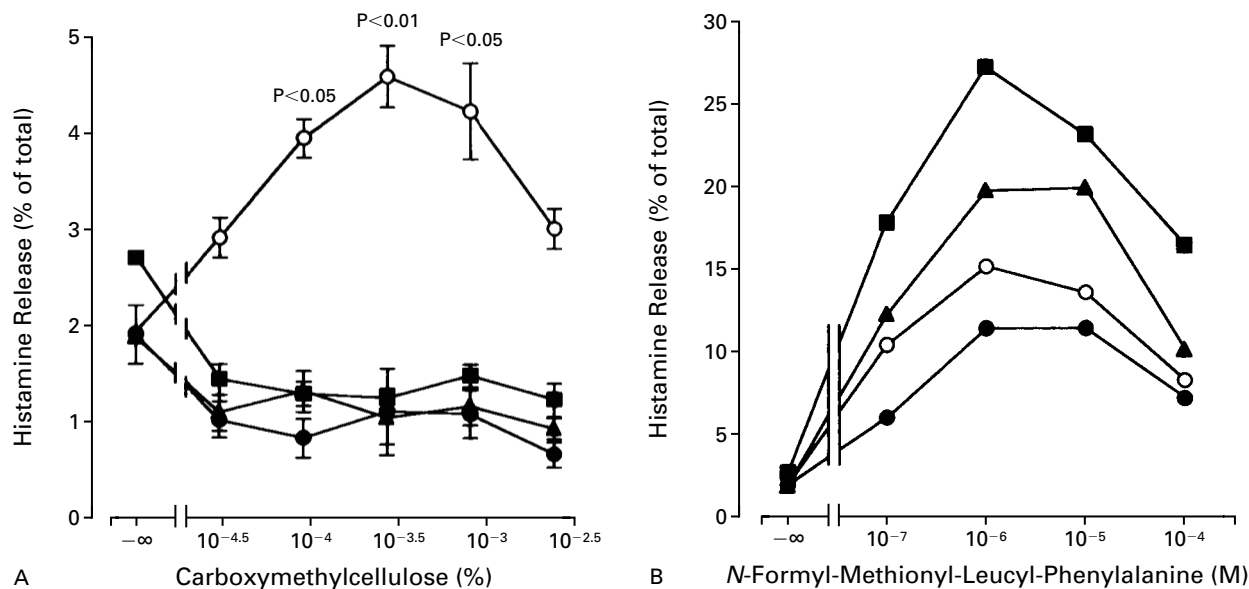


Figure 1. Release of Histamine from Leukocytes Induced by Carboxymethylcellulose Sodium or *N*-Formyl-Methionyl-Leucyl-Phenylalanine.

Leukocytes were isolated from peripheral-blood samples from the patient (○) and three normal subjects (●, ▲, and ■). Leukocytes were incubated for 5 minutes at 37°C before being exposed to carboxymethylcellulose sodium (Panel A) or *N*-formyl-methionyl-leucyl-phenylalanine (Panel B) for 15 minutes. Values in Panel A are the means (±SE) of three experiments, and values in Panel B are the means of two or three experiments. The P values indicate a significant difference as compared with the value in the absence of carboxymethylcellulose sodium (by analysis of variance followed by Dunnett's test).

Various allergic reactions to barium radiography have been reported. Pure barium sulfate is inert and nonantigenic, but various ingredients are added to improve the coating, flow, taste, and color of the suspension and to prevent settling, foaming, and flocculation. These ingredients are approved food additives; however, one of them, methylparaben, has been reported as causing an anaphylactic reaction after a barium enema.¹⁰ In our patient, skin testing identified carboxymethylcellulose sodium as the antigen causing the anaphylactic reaction. It also induced the release of histamine from leukocytes *in vitro*. The injection of penicillin or corticosteroids containing carboxymethylcellulose sodium has also been reported to induce an anaphylactic reaction in cattle and humans.²⁰⁻²²

Carboxymethylcellulose sodium is widely used as a suspending agent in pharmaceutical preparations, certain food products, and cosmetics. Therefore, previous exposure may have led to sensitization in our patient, although carboxymethylcellulose sodium is generally considered not to be absorbed. In summary, our patient had an anaphylactic reaction caused by the ingestion of carboxymethylcellulose sodium in barium sulfate suspension. Although not a common complication, such a reaction may occur in patients sensitized to carboxymethylcellulose sodium.

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