

Anaphylaxis to the Carbohydrate Carboxymethylcellulose in Parenteral Corticosteroid Preparations

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Key Words

Carboxymethylcellulose · Anaphylaxis · Oral provocation test · Cellular antigen stimulation test

Abstract

Background: Carboxymethylcellulose is a carbohydrate widely used as additive in tablets, cosmetics, some injectable hormone formulations, food (as E466) and as active principle in hydrocolloid dressings. Anaphylaxis to carboxymethylcellulose in parenteral corticosteroid preparations has previously been reported. Typically, skin tests were positive in such cases, occasionally specific IgE or histamine release have been demonstrated. **Case Report:** We report on 3 patients who suffered from anaphylactic symptoms after local injection of corticosteroid preparations. Intracutaneous skin tests with carboxymethylcellulose were positive; in 2, sulfidoleukotriene release could be measured in the cellular antigen stimulation test (CAST®). Specific IgE could not be identified. Oral provocation tests with typical doses of carboxymethylcellulose as found in food and tablets were negative. **Conclusion:** In patients with anaphylaxis to parenteral administration of carboxymethylcellulose, small amounts are tolerated by the oral route. Skin tests and CAST are useful diagnostic tools.

Introduction

Carboxymethylcellulose (E466) is a carbohydrate used in some formulations for parenteral administration of hydrophobic substances, e.g. corticosteroids. We describe 3 cases with anaphylaxis due to carboxymethylcellulose after parenteral injection of corticosteroid preparations. Intracutaneous tests were positive for carboxymethylcellulose, but not for the corticosteroid molecule or other additives. We performed lymphocyte stimulation (transformation) tests (LTT), cellular antigen stimulation tests (CAST®) and immunodot tests for specific IgE against carboxymethylcellulose. Only the CAST showed positive results, the other in vitro tests were negative. Carboxymethylcellulose is widely used as additive in other preparations such as tablets, cosmetics, food and radiography contrast media. Therefore, we performed an oral provocation test with carboxymethylcellulose to test whether only the parenteral application or also the oral intake could induce anaphylaxis. All patients tolerated an oral provocation test with carboxymethylcellulose with cumulative doses of 136 and 250 mg, respectively. These results confirmed the tolerance of larger oral doses of carboxymethylcellulose and the anaphylactic reactions to small doses of this carbohydrate in parenteral formulations. The pathogenesis could not be completely

elucidated, the positive skin tests suggest an antibody-mediated reaction, but we were not able to demonstrate circulating specific IgE by the immunodot technique. The release of sulfidoleukotrienes in the CAST suggests that basophils may play an important role.

Case Reports

Case 1

A 76-year-old woman was suffering from acute lumboschialgia and received several times injections with corticosteroids and local anesthetics into the L₅/S₁ region. After 4 ml of a mixture of Xyloneural (containing: lidocaine hydrochloricum, methylparahydrobenzoate) and Kenacort® A 40 (containing: triamcinolone acetonide, alcohol benzyllicum, polysorbatum 80, carboxymethylcellulosum natricum) had been injected, she developed 30 min later generalized pruritus, urticaria, angioedema of the lips, tachycardia and hypotonia. After emergency treatment with systemic antihistamines and corticosteroids, the patient had an uneventful recovery.

Prick and intracutaneous tests with lidocaine HCl and methylparahydrobenzoate were negative. Prick tests with Kenacort (10 mg/ml) were also negative, but the intracutaneous testing with 0.1 mg/ml Kenacort revealed a positive skin reaction with a

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1018–8665/03/2071–0100\$19.50/0

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Table 1. Results of allergologic tests

Tested agent	Test	Patient 1	Patient 2	Patient 3
Kenacort®	prick test	negative (10 mg/ml)	n.d.	<i>positive</i> (10 mg/ml)
	i.c. test	<i>positive</i> (0.1 mg/ml)	n.d.	<i>positive</i> (0.1 mg/ml)
Triamcort®	prick test	n.d.	negative (10 mg/ml)	n.d.
	i.c. test	n.d.	<i>positive</i> (0.1 mg/ml)	n.d.
Diprophos®	prick test	n.d.	n.d.	<i>positive</i>
	i.c. test	n.d.	n.d.	<i>positive</i>
Carboxymethylcellulose	prick test	negative (7.5 µg/ml)	negative (10 µg/ml)	<i>equivocal</i> (7.5 µg/ml)
	i.c. test	<i>positive</i> (0.075 µg/ml)	<i>positive</i> (1 µg/ml)	<i>positive</i> (0.075 µg/ml)
	CAST	negative	<i>positive</i>	<i>positive</i>
	LTT	negative	n.d.	n.d.
	OPT	negative (136 mg)	negative (250 mg)	negative (250 mg)
	specific IgE	negative	negative	negative

OPT = Oral provocation test; i.c. = intracutaneous; n.d. = not done.

wheal and erythema. Then, skin tests with each ingredient of Kenacort were performed. Prick and intracutaneous tests with triamcinolone acetonide, benzyl alcohol and polysorbate 80 were negative. The prick test with 7.5 µg/ml carboxymethylcellulose was negative. An intracutaneous test with 0.075 µg/ml carboxymethylcellulose was positive. To support these observations we also performed in vitro tests with the ingredients of Kenacort. The LTT did not show any stimulation with sodium carboxymethylcellulose, polysorbate 80 or benzyl alcohol. There was no significant release of sulfidoleukotrienes in the CAST after incubation with these ingredients either. Finally, after obtaining informed consent, a blinded oral provocation test with carboxymethylcellulose was performed. The patient tolerated a cumulative dose of 136 mg sodium carboxymethylcellulose without reaction. Specific IgE against carboxymethylcellulose were not detectable by the immunodot method (table 1).

Case 2

A 37-year-old man received an intra-articular injection of carbostesin (containing: bupivacainum hydrochloridum anhydricum) and Triamcort-Depot® (containing: triamcinolone acetonide, alcohol benzylicum, polysorbatum 80, carboxymethylcellulosum natricum) into the shoulder joint. Thirty minutes after the injection, the patient experienced a generalized urticaria, angioedema of the lips, dizziness and breathing

problems. A systemic emergency treatment was immediately given, and the patient quickly recovered. Prick and intracutaneous tests with bupivacain HCl and methylparahydrobenzoate were negative. A prick test with Triamcort (10 mg/ml) was also negative, but the intracutaneous test with 0.1 mg/ml Triamcort revealed a positive skin reaction with a wheal and erythema. The prick test with 10 µg/ml carboxymethylcellulose was negative, the intracutaneous test with 1 µg/ml carboxymethylcellulose was positive. An oral provocation test was performed, the patient tolerated a cumulative dose of 250 mg sodium carboxymethylcellulose without any reaction. The CAST with carboxymethylcellulose was clearly positive; however, it was not possible to measure specific IgE against carboxymethylcellulose by the immunodot technique (table 1).

Case 3

A 59-year-old man received an injection of lidocaine 1% (containing: lidocainum hydrochloricum anhydricum) and Diprophos® (containing: betamethasoni dipropionas, alcohol benzylicum, polysorbatum 80, carboxymethylcellulosum natricum, macrogolum 4000) into the right elbow. Thirty minutes after the injection, the patient experienced sweating, flush with generalized pruritus, nausea and a collapse which lasted a few minutes. The patient recovered without emergency treatment. Later at home a relapse occurred with angioedema of the feet and of the lips. Previous injections with cor-

ticosteroids and local anesthetics had been tolerated. Prick and intracutaneous tests with different local anesthetics and the additives were negative. Prick and intracutaneous tests with several parenteral corticosteroid preparations such as Kenacort (triamcinoloni acetonidum with caboxymethylcellulose), Solu-Medrol® (methylprednisolone without carboxymethylcellulose), Solu-Cortef® (hydrocortisone without carboxymethylcellulose), Celestone® (betamethasone without carboxymethylcellulose), Decadrone phosphate® (dexamethasone without carboxymethylcellulose) and Diprophos were performed. Prick tests for Kenacort and Diprophos were weakly positive, intracutaneous tests were clearly positive with a wheal and erythema. There was no reaction to the other steroid preparations. The prick test with 7.5 µg/ml carboxymethylcellulose was equivocal, and the intracutaneous test with 0.075 µg/ml was strongly positive. The patient tolerated a cumulative dose of 250 mg sodium carboxymethylcellulose in the oral provocation test without any symptoms. The CAST with carboxymethylcellulose revealed a significant release of sulfidoleukotrienes. The immunodot test to measure specific IgE was negative (table 1).

Skin tests with carboxymethylcellulose in 5 controls were negative.

Discussion

Carboxymethylcellulose is a highly viscous carbohydrate. It is used in injectable preparations as a suspending agent to promote solubilization of compounds with poor water solubility. These include corticosteroids, hormones like LHRH or somatostatin. Carboxymethylcellulose is also present in tablets as binder, glidant and antiadherent, in bulk laxatives as active principle and as an additive in food products. In food, carboxymethylcellulose is labeled as E466. Carboxymethylcellulose is also used in cosmetics as adsorbent, anticaking agent, emulsion stabilizer, bulking agent and viscosity-increasing agent, and it is the osmotically active ingredient in some hydrocolloid wound dressings.

There are several reports on anaphylactic reactions due to carboxymethylcellulose in injectable corticosteroids [1–7]. The symptoms included generalized pruritus, urticaria, angioedema, hypotension, dyspnea, vomiting and loss of consciousness. In all cases, when performed, skin tests with carboxymethylcellulose were positive, in some also histamine release tests [3, 8]. Another medically important source of carboxymethylcellulose are oral radiographic contrast media. One report describes an anaphylactic reaction after an upper gastrointestinal examination with carboxymethylcellulose-containing barium sulfate. In this patient, skin tests revealed carboxymethylcellulose as responsible for the anaphylaxis [8]. This report is of interest because it describes anaphylaxis after orally administered carboxymethylcellulose, whereas our patients did not react to the oral application of a small amount of carboxymethylcellulose as it is typically present in food and tablets. However, we recommend that our patients should not receive any radiographic contrast media containing

large amounts of carboxymethylcellulose, which increases the possibility that it may be absorbed.

Carboxymethylcellulose is commonly used as osmotic agent in hydrocolloid wound dressings. Johnsson and Fiskerstrand [9] described a patient with generalized urticaria and nausea due to carboxymethylcellulose in a hydrocolloid dressing. Because hydrocolloid dressings are often used in wound care, more such cases could occur in the future. Patients with contact urticaria to hydrocolloid dressings should be tested with carboxymethylcellulose and in the case of sensitization should avoid injectable drugs containing carboxymethylcellulose. Hamada and Horiguchi [10] described an allergic contact dermatitis of the hands due to carboxymethylcellulose in processed food in a bakery, indicating the importance of carboxymethylcellulose as food additive and suggesting that delayed-type hypersensitivity can occur as well. Carboxymethylcellulose as allergen also plays a role in animals. The important role of carboxymethylcellulose as allergen was already emphasized by de Weck and Schneider [11] in 1972. Aitken [12] found that cattle were more readily sensitized than guinea pigs to this carbohydrate; Freund's adjuvant enhanced sensitization, but was not essential. Straub et al. [13] described sensitization in horses to a product containing dexamethasone and carboxymethylcellulose. Hamajima et al. [14] used carboxymethylcellulose to enhance the production of specific antibodies and cell-mediated immunity against intranasally applied HIV DNA vaccine in mice.

So far, it has not been reported that LTT or CAST have been performed in patients with anaphylaxis to carboxymethylcellulose. The negative results in the LTT could be due to problems with the sensitivity of this in vitro test; alternatively the reaction against

this carbohydrate might not involve a T-cell-mediated immune response. However, 2 of the 3 patients revealed a release of sulfido-leukotrienes in the CAST suggesting that the anaphylactic reaction involves the release of mediators from basophil cells. The immunodot assays to detect specific IgE were negative. In another study, however, immunoassays and immunoblots revealed specific IgE to carboxymethylcellulose [4]. This implies that probably the sensitivity of our test is low or, alternatively, that the reaction is not mediated by IgE, but that specific IgG against carboxymethylcellulose could be involved. Thus, anaphylactic reactions to carbohydrates due to immune-complex reactions with high titers of IgG against dextrans have been described [15].

Our case reports demonstrate that anaphylactic reactions to carboxymethylcellulose are of practical importance, particularly since carboxymethylcellulose is present in some injectable hormone preparations, but also in radiographic contrast media, hydrocolloid dressings, oral medications and in food as additive E466. Therefore, we suggest to perform an oral provocation test in all patients with positive skin tests against carboxymethylcellulose to exclude a reaction to small oral doses of this widely used carbohydrate. Furthermore the application of the CAST to diagnose a reactivity to carboxymethylcellulose in vitro may be useful.

Acknowledgements

We thank the Allergy Laboratory (Prof. B. Przybilla) of the Dermatology Clinic, Ludwig Maximilian University, Munich, Germany, for the performance of the immunodot tests.

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