Cross-reactivity to Hydroxypropyl Methylcellulose and Hydroxyethyl Cellulose in a Patient Allergic to Carboxymethylcellulose: A Case Report

Méar A[1], Babin M[2], Tisserand F[3], André C[1], Beriziky P[4], Maillard H[1]

[1]*Service de Dermatologie, Centre Hospitalier du Mans, Le Mans, France*

[2]*Centre régional de pharmacovigilance, Centre Hospitalier Universitaire d'Angers, Angers, France*

[3]*Pôle de gestion des produits de soins, Pharmacie, Centre Hospitalier du Mans, Le Mans, France*

[4]*Département de Pneumologie-Allergologie, Centre Hospitalier Universitaire d'Angers, Angers, France*

J Investig Allergol Clin Immunol 2024; Vol. 34(6): 425-426
doi: 10.18176/jiaci.1019

Key words: Anaphylaxis. Carboxymethylcellulose. Hydroxypropyl methylcellulose. Hydroxyethyl cellulose. Excipients.

Palabras clave: Anafilaxia. Carboximetilcelulosa. Hidroxipropilmetilcelulosa. Hidroxietilcelulosa. Excipientes.

Carboxymethylcellulose (CMC), or carmellose, is a cellulose derivative used as a suspending agent in injectable preparations and artificial tears. It is also used in many medical, cosmetic, and food products as a binding, emulsifying, and antiadherent agent.

Anaphylaxis to CMC is rare, although IgE-mediated allergy to this molecule has already been proven [1,2]. These reactions can occur after administration of parenteral corticosteroid preparations [3,4], oral drugs (croscarmellose sodium) [5], eye drops [6], and hydrocolloid dressings and after food consumption [4,7,8].

Although cross-reactivity between CMC and other cellulose derivatives has been suspected [9,10], it has not been demonstrated previously.

In January 2023, a 71-year-old man was referred to our allergy unit for assessment of 3 episodes of suspected drug anaphylaxis. His previous history included complete prostatectomy for a Gleason 7 prostatic tumor, which had lately relapsed and was treated by radiotherapy, atrial fibrillation, recurring renal colic, chronic rhinitis, and atopic dermatitis.

In January 2018, he received an injectable suspension of betamethasone dipropionate (Diprostene) for knee arthrosis. Fifteen minutes after the injection, he experienced urticaria, facial edema, dysphagia, tachycardia, and persistent hypotension. The symptoms resolved after treatment with antihistamine, methylprednisolone, and injectable epinephrine.

On October 25, 2022, the patient received a first injection of triptorelin (Decapeptyl) for the treatment of a prostatic tumor. Ten minutes later, he experienced urticaria, facial edema, dyspnea, upper airway edema, and hypotension. He was treated with methylprednisolone and epinephrine.

Diprostene and Decapeptyl both include CMC as an excipient.

On December 27, 2022, the patient underwent placement of a double J stent with general anesthetic. During the intervention, he received sufentanil, propofol, lidocaine, ketamine, droperidol, cefazoline, tramadol, nefopam, and paracetamol. While leaving the operating room, the patient developed a rash, which disappeared after injection of antihistamine. No other symptoms of anaphylaxis were recorded. None of the abovementioned treatments contained CMC or cellulose derivatives as an excipient. In hindsight, the use of a urethral lubricant gel is probable, although this was not mentioned in the anesthesia report.

On January 24, 2023, skin prick tests and intradermal tests were performed to the highest nonirritant concentrations recommended by the European Academy of Allergy and Clinical Immunology for all the drugs, except triptorelin, which was not available. CMC was tested at 5 mg/mL (Celluvisc eye drops). Skin prick tests were positive for CMC (wheal of 5 mm and erythema of 20 mm) and betamethasone dipropionate containing CMC as an excipient (Diprostene; wheal of 4 mm and erythema of 25 mm). All other tests were negative. Following these tests, we diagnosed IgE-mediated allergy to CMC, and the patient was provided with an allergy pass.

On February 13, 2023, the patient underwent a double J stent replacement and ureteroscopy. He received several anesthetic drugs, none of which contained CMC or cellulose derivatives. One hour later, he received an injection of iobitridol. Immediately after, he developed hypotension, bronchospasm, and urticaria. Norepinephrine, epinephrine, and salbutamol were administered, and the patient recovered. He was referred to our department with suspected anaphylaxis to iobitridol. After further inquiries, we learned that a lidocaine urethral lubricant gel containing hydroxypropyl methylcellulose (HPMC) had been administered simultaneously with iobitridol, which is probably also what happened on December 27, 2022. Skin tests were performed and were negative for all anesthetic drugs and iobitridol, but positive for the culprit urethral lubricant gel (wheal of 4 mm and erythema of 10 mm). A prick test with a lidocaine urethral lubricant containing hydroxyethyl cellulose (HEC) as an excipient (Instillagel) also yielded positive results twice (wheal of 4 mm and erythema of 4 mm).

Injectable lidocaine (which does not contain a CMC derivative as an excipient) and iobitridol were administered under supervision without reaction, thus proving the absence of allergy to these drugs.

The double J stent was removed without urethral lubricant on March 01, 2023, and the patient presented no adverse reaction.

The patient has not avoided specific foods since the discovery of his allergy. As he presented no adverse reaction, we assumed that he tolerates oral intakes of small amounts of CMC derivatives. However, he was advised to see an allergist immediately if he experienced allergy symptoms after eating in the future.

To our knowledge, this is the first report of cross-reactivity to CMC, HPMC, and HEC proved by positive prick tests and unintentional provocation tests with CMC and HPMC.

Munk et al [10] report a case of anaphylaxis to HPMC in eyedrops during cataract surgery, with positive skin test results for HPMC and methylcellulose. No provocation tests with methylcellulose were performed because of the risk of anaphylaxis. Test results were negative for CMC.

Moreau et al [9] reported a case of contact urticaria to CMC in white chalk, with a positive prick test result for CMC. The patient also had urticaria with chalk containing HEC, although prick tests were negative for HEC.

This case was reported to the French Pharmacovigilance System, whose database contained no cases of cross-reactivity between drugs containing CMC and other CMC derivatives.

The present case illustrates, first, the importance of extensive investigation of allergens when several drugs are administered simultaneously in order not to miss the culprit allergen, and secondly, the importance of extensive investigation of allergens when CMC allergy is identified.

The patient currently tolerates cellulose derivatives in food. However, a case described by Townsend et al [4] shows that patients can develop a secondary oral allergy when they were initially allergic only through parenteral administration. Patients should therefore be warned of this possibility.

Likewise, as CMC derivatives can be found in hydrocolloid dressings and lubricant gels, the mucosa should be considered a surface that is potentially exposed to CMC derivatives.

The patient gave his consent for the publication of this case report.

The information provided in the present case report does not represent the opinion of the Agence Nationale de Sécurité du Médicament et des Produits de Santé (National Agency for the Safety of Medicines and Health Products).

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Niwa Y, Hayama K, Tagui T, Ito-Watanabe M, Endo T, Fujita H, et al. Case of anaphylaxis due to carmellose sodium. J Dermatol. 2019;47(1):15-7.
2. Galan C, Arrien de Lecea A, Bartolomé Zavala B, Pérez Escalera M, Sanchez de Vicente J. Immediate Hypersensitivity to Parenteral Corticosteroids Caused by IgE-Mediated Allergy to Carmellose. J Investig Allergol Clin Immunol. 2024;34(2):143-5.
3. Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the Carbohydrate Carboxymethylcellulose in Parenteral Corticosteroid Preparations. Dermatology. 2003;207(1):100-3.
4. Townsend K, Laffan J, Hayman G. Carboxymethylcellulose excipient allergy: a case report. J Med Case Rep. 2021;15(1):565.
5. Mumoli M, Cei M, Luschi R, Carmignani G, Camaiti A. Allergic reaction to Croscarmellose sodium used as excipient of a generic drug. QJM. 2011;104(8):709-10.
6. Carbonell A, Miralles JC, Escudero AI, Martinez A, Pineda F, Aldana D. Urticaria-angioedema Due to Carboxymethylcellulose Eye Drops. J Investig Allergol Clin Immunol. 2012;22(4):288-9.
7. Brockow K, Bauerdorf F, Kugler C, Darsow U, Biedermann T. «Idiopathic» anaphylaxis caused by carboxymethylcellulose in ice cream. J Allergy Clin Immunol Pract. 2021;9(1):555-7.
8. Ohnishi A, Hashimoto K, Ozono E, Sasaki M, Sakamoto A, Tashiro K, et al. Anaphylaxis to Carboxymethylcellulose: Add Food Additives to the List of Elicitors. Pediatrics. 2019;143(3):e20181180.
9. Moreau L, Alomer G, Dube N, Sasseville D. Contact Urticaria from Carboxymethylcellulose in White Chalk. Dermatitis. 2006;17(1):29-31.
10. Munk S, Heegaard S, Mosbech H, Garvey L. Two episodes of anaphylaxis following exposure to hydroxypropyl methylcellulose during catarac surgery. J Cataract Refract Surg. 2013;39(6):948-51.

Manuscript received May 7, 2024; accepted for publication May 23, 2024.

Amélie Méar
Service de Dermatologie
Centre Hospitalier du Mans
194 avenue Rubillard
72037 Le Mans, CEDEX 9
France
E-mail: amear@ch-lemans.fr

