

Two episodes of anaphylaxis following exposure to hydroxypropyl methylcellulose during cataract surgery

Sofie J. Munk, MD, Steffen Heegaard, MD, DMSc, Holger Mosbech, MD, DMSc,
Lene H. Garvey, MD, PhD

We report a case of immediate severe anaphylaxis to hydroxypropyl methylcellulose (HPMC) on 2 separate occasions during cataract surgery in a 71-year-old patient. Skin prick tests were positive for HPMC, a constituent of Ocucoat and Xylocaine gel, which were administered intraocularly during surgery. Skin prick tests were also positive for methylcellulose. Based on symptoms and clinical signs of anaphylaxis following 2 separate cataract operations together with positive prick tests to HPMC, HPMC is the most plausible cause of the reactions. The patient has since had uneventful surgery for a detached retina avoiding HPMC. This case stresses the importance of considering all medication given to patients as possible causes of an anaphylactic reaction.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2013; ■:■–■ © 2013 ASCRS and ESCRS

Anaphylaxis during or after cataract surgery due to instillation of drugs has been reported sporadically.^{1–4} Causes include injection of cefuroxime into the anterior chamber,¹ topical fluorescein sodium 2% eye-drops,² topical treatment with eyedrops containing neomycin,³ and hyaluronidase in a peribulbar block.⁴ Numerous drugs are administered during and after cataract surgery, making it impossible to immediately identify the exact cause of the anaphylaxis. Subsequent allergen investigation is necessary to find the causative agent and thereby prevent future exposure.

Hydroxypropyl methylcellulose (HPMC), also known as hypromellose, is a synthetic derivative of naturally occurring cellulose, a cellulose ether. This

compound is a listed food additive (E464) and is used for thickening and emulsifying liquids. In oral drugs, it is used in the production of hydrophilic matrices, which control and increase the duration of drug release to prolong the therapeutic effect,⁵ and as a coating material in micropellets for controlled release.⁶ It is also used in capsule shells for oral, inhalation, vaginal, and rectal administration.⁷ In topical hydrogel formulations, it acts as a gelling agent to control the release of the active substance⁸ and to optimize viscosity in ophthalmic suspensions.⁹ It is also an excipient in artificial tears for dry-eye treatment.¹⁰

Although several cases of anaphylactic reactions to carboxymethylcellulose have been reported,^{11–15} anaphylaxis caused by HPMC has not been reported previously.

CASE REPORT

A 71-year-old man with no relevant medical history, atopy, or previous history of allergic reactions developed anaphylaxis on 2 separate occasions immediately following cataract surgery. The first incident (October 2009) occurred while the patient was being transported home after cataract surgery in the left eye. He experienced severe palmar itching, dizziness, abdominal pain, nausea, and vomiting. He also felt swelling in his throat and developed urticaria on his neck and chest. On arrival home, the patient collapsed on the floor, semiconscious, and was subsequently admitted to the hospital, where he was treated with inhalation of adrenaline, antihistamine, and steroids. The symptoms resolved completely,

Submitted: January 25, 2013.

Accepted: February 7, 2013.

From the Eye Pathology Institute (Munk, Heegaard), Department of Neuroscience and Pharmacology, University of Copenhagen, the Department of Ophthalmology (Heegaard), University of Copenhagen, Glostrup Hospital, and the Danish Anaesthesia Allergy Centre (Mosbech, Garvey), Allergy Clinic, Copenhagen University Hospital, Gentofte, Copenhagen, Denmark.

Corresponding author: Lene H. Garvey MD, PhD, Danish Anaesthesia Allergy Centre, Allergy Clinic, Gentofte Hospital, Niels Andersens Vej 65, DK-2900 Hellerup, Denmark. E-mail: lene.heise.garvey@regionh.dk.

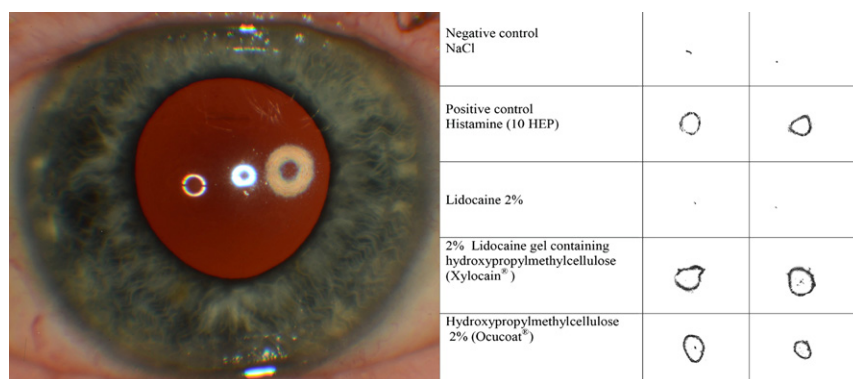


Figure 1. *Left:* Shortly after cataract surgery in the left eye, the patient developed an anaphylactic reaction. *Right:* Positive skin prick tests to Xylocaine gel and Ocucoat containing HPMC. Prick test with pure lidocaine was negative, ruling out allergy to the local anesthetic component.

and the patient was discharged from the hospital the same day. No further investigation into the cause of the anaphylactic reaction was performed.

Two years later (October 2011), cataract surgery was planned for the right eye by the same surgeon. Suspecting that the former anaphylactic reaction had been caused by the antibiotics used during surgery (intravenous cefuroxime and ciprofloxacin gel 3% applied locally), the surgeon changed to intravenous gentamicin and chloramphenicol 1% applied locally but otherwise used the same premedication and followed the same procedure as in the previous operation. In the waiting room, shortly after surgery was completed, the patient developed a generalized itchy rash and became acutely unwell, with excessive mucous production, nausea, vomiting, and abdominal pain. An ambulance was called. He was hypotensive at 74/41 mm Hg. On treatment with fluids, intravenous antihistamines, and steroids, his condition improved. On arrival at the hospital, the patient was stable but felt nauseated and had generalized urticaria. He recovered, was discharged the following day,

and referred to the Danish Anaesthesia Allergy Centre for investigation. The surgical result was not affected by the anaphylactic incident (Figure 1, left).

A list of all medications used during both cataract operations was obtained. These included local anesthesia agents, antiinflammatory drugs, lubricants and fillers mainly as eyedrops or gels. The patient was tested for the medications used in both procedures (Table 1). Skin prick tests with Ocucoat, which is formulated from a HPMC 2%, and to Xylocaine 2% gel, which also contains HPMC, were positive (Figure 1, right). Both these drugs had been administered during both operations. All other drugs used during the operations tested negative. To exclude possible cross-reactivity, other celluloses were tested. The patient tested positive to methylcellulose 2%, whereas a prick test with Diprosan (containing carboxymethylcellulose) was inconclusive and with Instillagel (containing hydroxyl ethylcellulose) was negative.

The patient was subsequently tested with various pure preparations of celluloses (Table 1). Again, skin tests for HPMC and methylcellulose 2% were strongly positive.

Table 1. Results of allergy testing.

Product	Skin Prick Test	Intradermal Test	Provocation	Specific IgE
Products used during both operations				
HPMC 2% (Ocucoat)	+	NT	NT	NT
Lidocaine 2% gel containing HPMC (Xylocaine)	+	NT	NT	NT
Ethylene oxide	NT	NT	NT	–
Latex	–	NT	NT	–
Chlorhexidine digluconate	–	–	NT	–
Lidocaine without adrenaline	–	–	– (sc)	NT
Cyclopentolate (Cyclogyl)	–	NT	NT	NT
Oxybuprocain (Novesine)	–	NT	NT	NT
Phenylephrine (Neosynephrin POS 10%)	–	–	– (iv)	NT
Triazolam	NT	NT	– (po)	NT
Diclofenac	–	–	– (po)	NT
Diclofenac eyedrops (Difen- Stulln)	–	NT	NT	NT
Other products containing celluloses				
Eye drops containing HPMC 3.2 mg/mL (Artelac)	+	NT	NT	NT
Methylcellulose 2%	+ / +	NT	NT	NT
Carboxymethylcellulose 7 mg/mL (Diprosan)	? / –	NT	NT	NT
Hydroxyl ethylcellulose (Instillagel)	– / ?	NT	NT	NT
Eyedrops containing carboxymethylcellulose 10 mg/mL (Celluvisc)	–	NT	NT	NT

+ = positive test; – = negative test; ? = inconclusive test; IgE = immunoglobulin E; iv = intravenous; NT = not tested; po = per oral; sc = subcutaneous

This time, the skin prick test was negative for carboxymethylcellulose and inconclusive for hydroxyl ethylcellulose. Blood samples were taken to perform histamine-release testing (HR-test) to the celluloses that were applied in the prick test (Table 1). Unfortunately, the patient was a non-responder to the HR-test; ie, the test was inconclusive. As a specific immunoglobulin E assay is not commercially available, the skin test results could not be supplemented with in vitro diagnostics.

DISCUSSION

To our knowledge, this is the first report of severe anaphylaxis presumed to be caused by sensitization to HPMC based on positive skin prick test results. Intradermal administration and provocation testing were considered to increase test sensitivity but were deemed unsafe since anaphylaxis has been reported following these tests.^{16,17} The widespread use of HPMC in medical preparations indicates that the risk for developing anaphylactic reactions at exposure is very low. Reactions have been described to carboxymethylcellulose in eyedrops,¹⁵ in depot injections of steroids,^{11-13,18-25} and to the carboxymethylcellulose component of barium sulfate suspension.^{14,26}

Cross-reactivity between celluloses has been examined in 3 cases of delayed reaction to carboxymethylcellulose²⁷ and in 2 cases of anaphylaxis to carboxymethylcellulose.²⁰ No cross-reactivity between carboxymethylcellulose and HPMC has been demonstrated.

Since HPMC is a constituent in many food and drug preparations and since our patient had no allergic symptoms except the 2 anaphylactic episodes, one can assume that he tolerates oral intake of small amounts of HPMC and other celluloses. Bigliardi et al.¹³ performed oral provocation tests with small doses of carboxymethylcellulose in 3 patients with anaphylaxis to parenteral administration of carboxymethylcellulose. All patients tolerated oral provocation with typical doses of carboxymethylcellulose found in food and tablets.

As we had to rely on skin prick tests as the only diagnostic method, we could not achieve conclusive results on possible cross-reactivity and chose to warn against parenteral administration of methyl and ethyl celluloses. At the end of the investigation, an "allergy pass" was issued to the patient. The allergy pass rapidly proved helpful as the patient was admitted to the hospital a few weeks later due to a retinal detachment. With the allergy pass, he avoided exposure to celluloses during surgery and the procedure was uneventful.

This case report illustrates the importance of detailed allergen investigation following an anaphylactic reaction during surgical procedures in which many drugs and substances are administered simultaneously. It also highlights the need for clinicians to

be aware of other causes of anaphylactic reactions besides those that are most self-evident.

REFERENCES

1. Villada JR, Vicente U, Javaloy J, Alió JL. Severe anaphylactic reaction after intracameral antibiotic administration during cataract surgery. *J Cataract Refract Surg* 2005; 31:620–621
2. Shahid H, Salmon JF. Anaphylactic response to topical fluorescein 2% eye drops: a case report. *J Med Case Rep* 2010; 4:27. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2837668/pdf/1752-1947-4-27.pdf>. Accessed February 9, 2013
3. Ansari IA, Onyema E. Severe generalised hypersensitivity reaction to topical neomycin after cataract surgery: a case report. *J Med Case Rep* 2008; 2:57. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267473/pdf/1752-1947-2-57.pdf>. Accessed February 9, 2013
4. Escolano F, Parés N, Gonzalez I, Castillo J, Valero A, Bartolomé B. Allergic reaction to hyaluronidase in cataract surgery. *Eur J Anaesthesiol* 2005; 22:729–730. Available at: http://journals.lww.com/ejanaesthesiology/Fulltext/2005/09000/Allergic_reaction_to_hyaluronidase_in_cataract.16.aspx. Accessed February 9, 2013
5. Li CL, Martini LG, Ford JL, Roberts M. The use of hypromellose in oral drug delivery. *J Pharm Pharmacol* 2005; 57:533–546. Available at: <http://onlinelibrary.wiley.com/doi/10.1211/0022357055957/pdf>. Accessed February 9, 2013
6. Rogers TL, Wallick D. Reviewing the use of ethylcellulose, methylcellulose and hypromellose in microencapsulation. Part 1: materials used to formulate microcapsules. *Drug Dev Ind Pharm* 2012; 38:129–157
7. Al-Tabakha MM. HPMC capsules: Current status and future prospects. *J Pharm Pharm Sci* 2010; 13:428–442. Available at: <http://ejournals.library.ualberta.ca/index.php/JPPS/article/viewFile/8870/7398>. Accessed February 9, 2013
8. Ji JA, Liu J, Shire SJ, Kamerzell TJ, Hong S, Billeci K, Shen Y, Wang YJ. Characteristics of rhVEGF release from topical hydrogel formulations. *Pharm Res* 2010; 27:644–654
9. Akram M, Shyum Naqvi SB, Gauhar S. Development of new ophthalmic suspension prednisolone acetate 1%. *Pak J Pharm Sci* 2010; 23:149–154. Available at: <http://www.vvvvvv.pjps.pk/CD-PJPS-23-2-10/Paper-5.pdf>. Accessed February 9, 2013
10. Doughty MJ, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic Physiol Opt* 2009; 29:573–583. Available at: <http://onlinelibrary.wiley.com/doi/10.1111/j.1475-1313.2009.00683.x/pdf>. Accessed February 9, 2013
11. Oppliger R, Hauser C. Anaphylaxie nach Injektion von Kortikosteroidpreparaten—Carboxymethylzellulose, ein verstecktes Allergen [Anaphylaxis after injection of corticosteroid preparations—carboxymethylcellulose as a hidden allergen]. *J Dtsch Dermatol Ges* 2004; 2:928–930
12. Schuster C, Wüthrich B, Hartmann K, Kuhn M. Anaphylaxis to E466. *Allergy* 2000; 55:303–304. Available at: <http://onlinelibrary.wiley.com/doi/10.1034/j.1398-9995.2000.00401.x/pdf>. Accessed February 9, 2013
13. Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. *Dermatology* 2003; 207:100–103
14. Dumond P, Franck P, Morisset M, Sainte LJ, Kanny G, Moneret-Vautrin DA. Pre-lethal anaphylaxis to carboxymethylcellulose confirmed by identification of specific IgE—review of the literature. *Eur Ann Allergy Clin Immunol* 2009; 41:171–176
15. Carbonell A, Miralles JC, Escudero AI, Martínez A, Pineda F, Aldana D. Urticaria-angioedema due to carboxymethylcellulose

- eye drops. *J Investig Allergol Clin Immunol* 2012; 22:288–289. Available at: <http://www.jiaci.org/issues/vol22issue4/8-21.pdf>. Accessed February 9, 2013
16. Vincent D, Ben Naoum Y, Chi HC, Hentschel V, Pradalier A. Systemic anaphylaxis induced by intradermal testing. *Allerg Immunol (Paris)* 2002; 34:45–46
 17. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; 57:45–51. Available at: <http://onlinelibrary.wiley.com/doi/10.1046/j.0105-4538.2001.00001.x-i8/pdf>. Accessed February 9, 2013
 18. Field S, Falvey E, Barry J, Bourke J. Type 1 hypersensitivity reaction to carboxymethylcellulose following intra-articular triamcinolone injection. *Contact Dermatitis* 2009; 61:302–303
 19. Al Hadithy A, van Maaren M, Vermes A. Anaphylactic reactions following Kenacort-A® injection: carboxymethylcellulose is involved once again. *Contact Dermatitis* 2011; 64:179–180
 20. Beaudouin E, Kanny G, Gueant JL, Moneret-Vautrin DA. Anaphylaxie a la carboxymethylcellulose: a propos de deux cas de chocs a des corticoides injectables. [Anaphylaxis caused by carboxymethylcellulose: report of 2 cases of shock from injectable corticoids]. *Allerg Immunol (Paris)* 1992; 24:333–335
 21. Patterson DL, Yunginger JW, Dunn WF, Jones RT, Hunt LW. Anaphylaxis induced by the carboxymethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). *Ann Allergy Asthma Immunol* 1995; 74:163–166
 22. Montoro J, Valero A, Elices A, Rubira N, Serra-Baldrich E, Amat P, Malet A. Anaphylactic shock after intra-articular injection of carboxymethylcellulose. *Allergol Immunopathol (Madr)* 2000; 28:332–333. Available at: <http://www.elsevier.es/sites/default/files/elsevier/pdf/105/105v28n06a90002127pdf001.pdf>. Accessed February 9, 2013
 23. Venturini M, Lobera T, del Pozo MD, Gonzalez I, Blasco A. Immediate hypersensitivity to corticosteroids. *J Investig Allergol Clin Immunol* 2006; 16:51–56. Available at: <http://www.jiaci.org/issues/vol16issue01/9.pdf>. Accessed February 9, 2013
 24. Laing ME, Fallis B, Murphy GM. Anaphylactic reaction to intralesional corticosteroid injection. *Contact Dermatitis* 2007; 57:132–133
 25. Murrieta-Aguttes M, Michelen V, Leynadier F, Duarte-Risselin C, Halpern GM, Dry J. Systemic allergic reactions to corticosteroids. *J Asthma* 1991; 28:329–339
 26. Muroi N, Nishibori M, Fujii T, Yamagata M, Hosoi S, Nakaya N, Saeki K, Henmi K. Anaphylaxis from the carboxymethylcellulose component of barium sulfate suspension. *N Engl J Med* 1997; 337:1275–1277. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJM199710303371804>. Accessed February 9, 2013
 27. Barbaud A, Waton J, Pinault AL, Bursztejn AC, Schmutz JL, Tréchet P. Cutaneous adverse drug reactions caused by delayed sensitization to carboxymethylcellulose. *Contact Dermatitis* 2011; 64:294–297