

consumption, HMWK cleavage, and C1Inh function alteration occurred in the very early phase, which is during the prodromal phase. Our patient was given an early treatment plan for subsequent angioedema attacks, which made it difficult to reproduce the same biological conditions as in the present study. Fortunately, we had the opportunity to study another patient through an impending attack, and the results were similar, showing cleavage of HMWK 7 hours before and during visible angioedema (data not shown). These findings are consistent with a systemic activation process before clinical expression of local angioedema, which is in line with a recent model.⁸ During this early phase, C1Inh control may be overcome by sustained activation of KKS proteases, whereas it takes time for the liver to counteract this proteolytic activity by production of C1Inh and proenzymes. This finding could explain why the highest spontaneous kininogenase activity and lowest plasma content of proenzymes were found before angioedema appearance. In addition, sustained protease and long reconstitution time of HMWK could account for the persisted high HMWK cleavage observed despite proenzyme reconstitution during visible angioedema.

Finally, our results could explain why in the Icatibant Outcome Survey early treatment with this selective β_2 -receptor antagonist resulted in shorter attack duration.⁹ Antagonists being expected to have a pronounced efficacy when the receptors are not fully occupied by their ligands.

By showing that local BK-AE occurred many hours after systemic KKS activation, this case shed new light on the pathogenesis of the disease. The prodromal phase may occur while vascular permeability process progresses toward angioedema phenotype. Therefore, biological diagnostic workup is of greatest value when performed at a very early phase of the attack.

Samuel Luyasu, MD*
Delphine Charignon, PharmD, PhD†
Denise Ponard, PharmD‡

Christian Drouet, PharmD, PhD†‡
Arije Ghannam, MD, PhD†
*Adult Emergency Department
Immuno-Allergology Department
Centre Hospitalier de Luxembourg
Luxembourg, Luxembourg
†Université Grenoble-Alpes
Grenoble, France
‡University Hospital
Grenoble, France
arije.ghannam@kininx.com

References

- [1] Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet*. 2006;79:1098–1104.
- [2] Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69:602–616.
- [3] Magerl M, Doumoulakis G, Kalkounou I, et al. Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. *Clin Exp Dermatol*. 2014;39:298–303.
- [4] Martin L, Renné T, Drouet C. Urticaria as a presenting prodromal manifestation of attacks of hereditary angioedema. *Acta Derm Venereol*. 2016;96:574–575.
- [5] Baroso R, Sellier P, Defendi F, et al. Kininogen cleavage assay: diagnostic assistance for kinin-mediated angioedema conditions. *PLoS ONE*. 2016;11:e0163958.
- [6] Defendi F, Charignon D, Ghannam A, et al. Enzymatic assays for the diagnosis of bradykinin-dependent angioedema. *PLoS ONE*. 2013;8:e70140.
- [7] Scott CF, Silver LD, Schapira M, Colman RW. Cleavage of human high molecular weight kininogen markedly enhances its coagulant activity: evidence that this molecule exists as a procofactor. *J Clin Invest*. 1984;73:954–962.
- [8] Hofman ZLM, Relan A, Zeerleder S, Drouet C, Zuraw B, Hack CE. Angioedema attacks in patients with hereditary angioedema: local manifestations of a systemic activation process. *J Allergy Clin Immunol*. 2016;138:359–366.
- [9] Maurer M, Aberer W, Bouillet L, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS ONE*. 2013;8:e53773.

Efficacy of a single dose of omalizumab for the prevention of ethylene oxide intraoperative anaphylaxis



Ethylene oxide (EtO) is a highly reactive gas commonly used to sterilize pharmaceutical and biomedical thermosensitive products, such as infusion sets, cannulae, intubation materials, ventriculoperitoneal shunts, dialysis catheters, and stents.¹ Albeit rare, allergic reactions to EtO can cause serious clinical symptoms in patients who have been repeatedly exposed to EtO-sterilized materials during medical procedures (ie, multiple operations, blood transfusions, hemodialytic treatment).^{2–4} Several cases of perioperative EtO-induced anaphylaxis in patients with myelomeningocele have been reported.¹

In a study of a population with spina bifida, Porri et al⁵ observed that 32% of children with this condition who developed perioperative anaphylaxis were sensitized to EtO. In a retrospective study, Pittman et al⁶ found a 23% prevalence of IgE antibodies against EtO among children with myelomeningocele, suggesting that these patients seem to be at an increased risk of sensitization. The literature is, however, scant, and no recent data are currently available.

We describe a 24-year-old man born in 1994 with congenital hydrocephalus and spastic tetraplegia who has had numerous

corrective surgical procedures since birth. At 3 years of age, this patient was referred to our clinic after experiencing intraoperative allergic reaction (erythema and laryngospasm) while under local anesthesia. He had no medical history of previous drug allergic reactions. The results of a skin prick test with latex extract and an IgE test (>100 U/mL) were markedly positive, thereby making a diagnosis of latex allergy possible. Latex-safe protocols were adopted in 2 further uneventful surgical procedures.

At the age of 19 (February 2013), the patient experienced an anaphylactic reaction (generalized urticaria and severe hypotension, as reported in the patient's medical record) in a latex-safe environment while under general anesthesia and receiving bisoprolol and amlodipine therapy. The reaction occurred approximately 2 hours after the administration of intravenous cefuroxime and necessitated resuscitation and the administration of adrenaline, corticosteroids, and antihistamines. During the subsequent diagnostic workup at 20 years of age (March 2014), skin prick tests, intradermal tests, and/or IgE measurement were performed with latex, EtO, and drugs used during the surgery (atropine, propofol, cisatracurium, and fentanyl). The allergologic workup, which was extended to include other related drugs, yielded a positive latex skin test result and negative results for skin prick tests and intradermal tests for general anesthetics (vecuronium, atracurium, cisatracurium, rocuronium, thiopental, fentanyl, propofol and

atropine), major and minor penicillin determinants, ampicillin, amoxicillin, ceftriaxone, cefuroxime, and ceftazidime.

The results of specific IgE testing (UniCap, ThermoFisher, Uppsala, Sweden) were positive for EtO (33.1 U/mL), latex specific IgE (5.9 U/mL), and, in particular, rHev b 5 (0.82 U/mL), rHev b 6.1 (4.15 U/mL), and rHev b 6.2 (4.17 U/mL). Specific IgE test results for penicilloyl V and G, amoxicillin, ampicillin, cephalosporin, formaldehyde, and gelatin were negative. The basal serum tryptase level (immunofluorimetric CAP assay, Unicap 100; ThermoFisher) was 8.3 µg/L (reference range, <11.5 µg/L). Tryptase levels were not measured during any of the previous allergic reactions. Total IgE (510 IU/mL) was dosed in May 2014, and measurement of specific IgE to EtO (34 U/mL) was repeated.

Lacking the certainty that no completely latex-safe environment had been provided, we retrospectively assessed possible latex contamination but were only able to ascertain the use of certain instruments sterilized with EtO. In August 2014, increased intracranial pressure that resulted from a ventriculocjugular shunt malfunction required urgent surgery. Given the elevated level of IgE-mediated EtO sensitization and the difficulty in arranging an EtO-safe surgical environment, a single, preoperative, 600-mg dose of omalizumab was subcutaneously administered, along with intravenous corticosteroids and antihistamines, 2 hours before latex-safe surgery. Nonexchangeable EtO-sterilized instruments were used during surgery. The omalizumab dose was selected based on the patient's weight (65 kg) and total IgE level (510 IU/mL), following the asthma dosage guidelines. Omalizumab was well tolerated with no adverse reactions; surgery was uneventful, and no reactions occurred during the postoperative follow-up.

One month after surgery, the total IgE level (813 U/mL) and specific IgE level for EtO (28.4 U/mL) and for latex (6.92 U/mL) were retested. Since then no further surgical procedures have been necessary.

Both the off-label use of omalizumab and submission of the case for publication have been approved by the Ethics Committee of the University Hospital of Ancona (Italy). In individuals undergoing numerous surgical procedures, in patients undergoing dialysis, or in individuals who underwent valve replacement and drainage, the onset of intraoperative anaphylactic reactions may have been related to EtO sensitization because EtO is widely used to sterilize various medical devices.

It is mandatory to look for EtO sensitivity in the diagnostic workup of patients who have had multiple procedures and developed an intraoperative allergic reaction. Because EtO sensitization may be associated with other sensitizations like that of latex, it is important to underline the needs to investigate all possible causes of intraoperative anaphylaxis.

Unlike latex allergy, the logistic and organizational difficulties involved in EtO-safe surgery are greater. No detailed standard procedures for preventive strategies exist. Moreover, any recommendations are based on a dated and scant number of retrospective studies and case reports.

Published strategies often included rinsing with sterile saline, prolonged storage time, plasma sterilization, and aeration to reduce residual levels of EtO. However, rinsing itself could cause contamination, and plasma sterilization cannot be used for material that contains cellulose. In addition, because surgical instruments cannot be sterilely repacked, they have to be sterilized shortly before

surgery.⁷ As a result, EtO-safe surgery is very difficult to arrange because of its widespread use, especially in surgical emergencies.

Under such circumstances, treatment with omalizumab can be considered as a preventive measure. Omalizumab is a monoclonal antibody that binds human IgE and reduces the expression of FcεRI on circulating basophils and mast cells. It is approved for the treatment of allergic asthma and chronic urticaria. Certain studies suggest that omalizumab may be efficient in treating patients with systemic mastocytosis and recurrent idiopathic anaphylaxis and in those who poorly tolerate venom immunotherapy.^{8,9} Given the urgent need for surgery in our patient, a single preoperative dose of omalizumab was administered with success.

To the best of our knowledge, omalizumab has only ever been used as preexposure preventive treatment in one EtO-sensitized patient with a history of intraoperative anaphylaxis. Injections were started 2 months before surgery; the dosage was calculated based on the patient's weight and total IgE level.⁷

Our case shows that a single preoperative dose of omalizumab could be a cost-convenient alternative to multiple doses and a viable option for emergency surgery in EtO-sensitized individuals with a history of intraoperative anaphylaxis. However, further studies are needed to evaluate the efficacy of this preventive short protocol on a larger patient population.

Maria Beatrice Bilò, MD*

Alice Corsi, MD†

M. Feliciano Brianzoni, MD*

M. Stella Garritani, MD*

Leonardo Antonicelli, MD*

*Allergy Unit

Department of Internal Medicine

University Hospital Ospedali Riuniti di Ancona

Ancona, Italy

†Postgraduate School of Allergy and Clinical Immunology

Università Politecnica delle Marche

Ancona, Italy

mariabeatrice.bilo@ospedaliriuniti.marche.it

References

- [1] Demontoux V, Moreau E, Peyron I, et al. Surgery in a patient allergic to ethylene oxide. *Pharm World Sci*. 2008;30:208–209.
- [2] Bache S, Petersen JT, Garvey LH. Anaphylaxis to ethylene oxide: a rare and overlooked phenomenon? *Acta Anaesthesiol Scand*. 2011;55:1279–1282.
- [3] Ebo DG, Bosmans JL, Couttenye MM, Stevens WJ. Haemodialysis-associated anaphylactic and anaphylactoid reactions. *Allergy*. 2006;61:211–220.
- [4] Belen B, Polat M. Type I allergic hypersensitivity reactions due to ethylene oxide sterilised leucocyte filters in patients with thalassaemia: report of four cases. *BMJ Case Rep*. 2015;2015:bcr2014208490.
- [5] Porri F, Pradal M, Lemièrre C, et al. Association between latex sensitization and repeated latex exposure in children. *Anesthesiology*. 1997;86:599–602.
- [6] Pittman T, Kiburz J, Steinhardt G, Krock J, Gabriel K. Ethylene oxide allergy in children with spina bifida. *J Allergy Clin Immunol*. 1995;96:486–488.
- [7] Listyo A, Hofmeier KS, Bandschapp O, Erb T, Hasler CC, Bircher AJ. Severe anaphylactic shock due to ethylene oxide in a patient with myelomeningocele: successful exposure prevention and pretreatment with omalizumab. *A Case Rep*. 2014;2:3–6.
- [8] Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. *J Investig Allergol Clin Immunol*. 2009;19:225–229.
- [9] Kibsgaard L, Skjold T, Deleuran M, Vestergaard C. Omalizumab induced remission of idiopathic anaphylaxis in a patient suffering from indolent systemic mastocytosis. *Acta Derm Venereol*. 2014;94:363–364.