

Clinical Letter

Non-IgE-dependent hypersensitivity to macrogol 6000

DOI: 10.1111/ddg.13479

Dear Editors,

In the pharmaceutical and cosmetic industry, macrogol (polyethylene glycol, PEG) is a frequently used drug and drug vehicle. Anaphylactoid and anaphylactic reactions to macrogol are uncommon, with only few reports published in the literature. We would like to present the following case: a few minutes after taking Vicks Nyquil® Cold and Flu Nighttime Relief Liquid, a 42-year-old woman experienced a grade 3 anaphylactic reaction including tachycardia, dyspnea, involuntary urination, and loss of consciousness. Independent of this event, she also reported grade 2 anaphylaxis – with urticaria, tachycardia, and dyspnea – following the use of GeloRevoice® lozenges. In addition, she subsequently reported a history of contact urticaria after application of the shaving gel Hawaii Feeling® as well as an ointment used for common cold (Eucabal balsam S®). The patient had no preexisting cardiovascular condition [1]. She had a history of allergic rhinoconjunctivitis with known sensitization to rye pollen.

Prick-to-prick testing using the implicated products was positive. For further diagnostic workup, the manufacturers of the aforementioned products were asked to provide a list of individual ingredients contained therein. Here, we were able to show a positive reaction to macrogol 6000 5 % at dilutions of 1:10 (10 mm/30 mm) and 1:100 (8 mm/30 mm) (Figure 1a, b). The numbers in brackets indicate the maximum diameter

of the wheal and the erythema. Open application testing using the shaving gel Hawaii Feeling® resulted in contact urticaria in the test area after ten minutes (Figure 1c). The validity of skin prick tests in our patient was limited as she exhibited urticarial dermatographism to saline (3 mm/7 mm). She had no known history of dermatographism, and there was no respective clinical relevance in everyday life. In order to rule out a nonspecific, irritant skin reaction to macrogol 6000, prick testing was also performed on a control subject (hospital employee), showing a negative reaction to macrogol 6000 5 % at dilutions of 1:10 and 1:100.

Basophil activation tests using macrogol 6000 at dilutions of 2.5 %, 0.25 %, 0.025 %, and 0.0025 % were negative. The positive controls FcR (anti-IgE, 85.2 % CD63-positive basophils, reference value > 10 %) and fMLP (49.3 % CD63-positive basophils, reference value > 10 %) showed normal stimulation, thus providing valid test results.

Blood tests showed total IgE levels of 270 kU/L and mast cell tryptase levels of 6.1 µg/L. To confirm the suspected intolerance to macrogol, the patient was admitted as an inpatient and subjected to oral, double-blind, placebo-controlled provocation testing with macrogol 6000. Due to generalized urticaria, the challenge test was terminated after a cumulative dose of 0.3 g (single doses of 0.1 g and 0.2 g given at a one-hour interval) (Figure 2). Symptoms fully resolved following intravenous administration of dimethindene maleate (4 mg) and prednisolone (total dose 500 mg). Based on history, clinical symptoms, diagnostic workup, and positive oral provocation testing with macrogol 6000, our patient was diagnosed with non-IgE-dependent hypersensitivity to macrogol 6000.

She was given an allergy ID card and an emergency kit [2] consisting of an epinephrine autoinjector (Fastjekt® 300 µg), an antihistamine without macrogol (loratadine 10 mg) and a

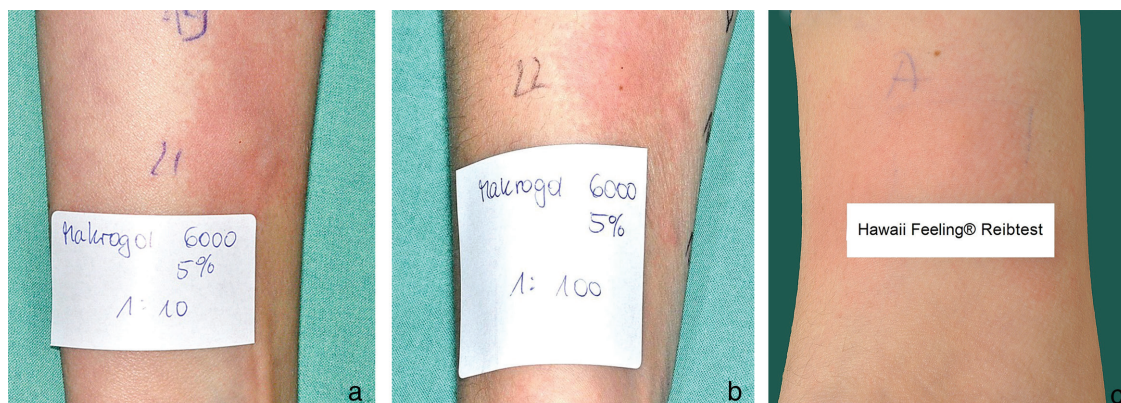


Figure 1 Skin prick-to-prick testing with macrogol 6000 5 % 1:10 (a) and 1:100 (b); contact urticaria caused by the shaving gel Hawaii Feeling® following open application testing (c).



Figure 2 Generalized urticaria following oral provocation with macrogol 6000 (0.3 g).

corticosteroid (prednisolone 50 mg). In addition, she was instructed about the occurrence of macrogol in various drugs, cosmetics, and industrial products.

Macrogol is a linear, long-chain, water-soluble, non-toxic polymer consisting of ethylene oxide groups with a molecular weight ranging from 200 to 35,000 g/mol [3]. The term polyethylene glycol is used for compounds with a higher molecular weight. Depending on the chain length, the substance is either liquid, paste-like, or solid. In medicine, it is used as a laxative agent prior to colonoscopy (macrogol 3350), as binding agent and additive in drugs, and as water-soluble ointment base ("macrogol ointment DAC"). In addition, it is found in numerous cosmetic products as well as in solvents, lubricants, and plasticizers [4, 5].

Given that commercially available antihistamines and corticosteroids also contain macrogol [6, 7], this presents an enormous risk for patients with anaphylactic or anaphylactoid reactions to macrogol as these agents are commonly given (and supposed to provide relief) in case of allergic reactions.

Both short-chain and long-chain macrogol appears to play a role in the development of hypersensitivity and anaphylactoid reactions. Even small amounts may lead to severe reactions [4]. Apart from C3b-dependent complement activation [6, 8], the induction of a specific IgE-dependent immune response has also been proposed. As yet, however, there has been no evidence of macrogol-specific IgE antibodies [4, 8].

In their 2016 review, Wenande and Garvey reported 74 immediate-type reactions to polyethylene glycol published in 37 case reports since 1977 [4]. Patient age ranged from 24 to 86 years. Systemic anaphylactic or anaphylactoid reactions occurred after oral ingestion as well as intraarticular, intramuscular, or intravenous injections. Apart from palmo-plantar pruritus, generalized urticaria, and angioedema, there were also grade 3 and 4 cardiovascular reactions with larynx edema, loss of consciousness, and anaphylactic shock. Severe reactions were reported in 20 % of the cases. Topical application to the skin and mucous membranes solely resulted in contact urticaria. Prick and intradermal testing was

frequently positive. In two cases, there were positive basophil activation tests [9, 10]. Histamine release tests were negative. Ethylene oxide-specific IgE antibodies were detected in none of these cases.

To date, three hypersensitivity reactions caused by macrogol have been reported to the European anaphylaxis registry (currently 8,541 registered cases) [11]. The upshot as regards everyday clinical practice is as follows: in case of unexplained anaphylactic reactions to chemically unrelated drugs, intolerance to additives should be considered and additional diagnostic tests be performed.

Conflict of interest

None.

Katja Berndt, Marvin Kuske, Stefan Beissert, Petra Spornraft-Ragaller, Andrea Bauer

Department of Dermatology, Carl Gustav Carus University Medical Center, Technical University Dresden, Germany

Correspondence to

Katja Berndt
Department of Dermatology
Carl Gustav Carus University Medical Center
Technical University Dresden

Fetscherstraße 74
01307 Dresden, Germany

E-mail: katja.berndt@uniklinikum-dresden.de

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