

Letter to the Editor

Inhibition of polyethylene glycol-induced histamine release by monomeric ethylene and diethylene glycol: A case of probable polyethylene glycol allergy

To the Editor:

Polyethylene glycols (PEGs) or macrogols are hydrophilic polyethers commonly used in pharmaceutical, cosmetic, food, and household products. Though primarily known as the active ingredient in colonoscopy lavages, PEGs also serve as solvents, excipients, and bulking and dispersing agents. Varying nomenclature exists: often appearing in the terminology is a number (eg, PEG 4000), denoting the rounded average molecular weight of the PEG chains in a given mixture.

PEGs are reported to display low toxicity and immunogenicity.^{1,2} However, following increased use within the past 2 decades, mild to severe hypersensitivity reactions have been described.³⁻⁸ The true prevalence of PEG sensitization is suspected to be higher than reported.⁴

We describe a unique case of allergy to PEGs. Results of skin prick test (SPT), basophil-histamine release (HR) test, and provocation, as well as HR inhibition using the monomer and dimer components of PEG, made IgE-mediated allergy to both low- and high-molecular-weight PEGs probable.

A 27-year-old woman was investigated following 3 consecutive allergic reactions of unknown etiology. She was atopic with confirmed allergy toward birch, grass, dust mites, and dog, suffering from rhinitis and asthma with a recent exacerbation during the grass-pollen season. She had been treated for anxiety with Effexor (venlafaxin containing PEG 400; Pfizer, Ballerup, Denmark). In addition, she had noted itching after the application of PEG-containing creams (Helosan; Pfizer/Carbamid; Meda OTC, Allerød, Denmark). She reported 2 cases of anaphylaxis 1 week apart: (1) following a Depo-Medrol (methylprednisolone acetate containing PEG 3350;

Pfizer) injection for seasonal allergic symptoms and (2) after the ingestion of a Balancid Novum (calcium carbonate magnesium hydroxide containing PEG 6000; Meda OTC) tablet for acid reflux. Symptoms were immediate-onset itching of throat and ears, hoarseness, hypotension, dizziness, generalized urticaria, and profuse vomiting. One week prior to the first anaphylactic episode, she experienced localized urticaria and palmoplantar pruritus during a tattoo procedure preceded by the application of Vaseline to the skin. Normal serum tryptase (1.35 µg/L) made an underlying mast cell disorder unlikely.

The initial aim was to exclude steroid allergy. A variety of steroid-based drugs were tested, while confirmation of hypersensitivity to the products implicated in the patient's allergic reactions was obtained via SPT and the HR test (Table I; Fig 1). Direct HR test (RefLab, Copenhagen, Denmark) involved the incubation of heparinized washed blood with 6 concentrations of each product. During incubation, basophil-released histamine was absorbed by glass microfiber-coated microtiter plates. Glassfiber-bound histamine was determined fluorometrically.⁹ In addition, passive sensitization of IgE-stripped, donor basophils with patient serum and subsequent challenge with Depo-Medrol and PEG 6000 was performed. Last, inhibition of direct HR was completed by preincubation of patient blood with monomeric and dimeric fractions of PEG (ethylene glycol and diethylene glycol) at a concentration of 2%.

PEGs of various chain lengths were suspected of being the common factor in the offending products. PEG-containing products the patient had been exposed to, pure PEG solutions of 2 molecular weights (PEG 3350 and PEG 6000), and the monomer and dimer fractions of PEG were investigated in SPT (Table I) and HR testing (Fig 1). Because of the severity of the patient's reactions, provocation and intradermal tests were deemed too hazardous, as systemic reactions have been reported following similar testing.^{6,7}

TABLE I. SPT, HR test, and provocation results

Product	SPT*	HR test†	Provocation
Steroid testing			
Methylprednisolone acetate (Depo-Medrol) contains PEG 3350	Wheal size (mm)		
0.4 mg/mL	6	NT	NT
4 mg/mL	10	+	NT
40 mg/mL	15	+	NT
Methylprednisolone succinate 40 mg/mL (Solu-Medrol) does not contain PEG	÷	÷	NT
Prednisolone 25 mg does not contain PEG	NT	NT	÷ (po)
Fluticasonefuroate (Avamys) does not contain PEG	÷	NT	÷ (Intranasal)
PEG-containing product testing			
Carbamid cream contains PEG 1500	4	NT	NT
Helosan cream contains PEG 100-stearate	5	NT	NT
Balancid Novum contains PEG 6000	7	+	NT
PEG 3350 1:10 v/w in aqueous solution (Moviprep A, Orifarm A/S, Odense, Denmark)	9	+	NT
PEG 6000 1:1 v/w in aqueous solution (Sigma-Aldrich A/S, Brøndby, Denmark)	12	+	NT
Ethylene glycol monomer/dimer testing			
Ethylene glycol (monomer fraction) (undiluted) (Sigma-Aldrich A/S)	÷	÷	NT
Diethylene glycol (dimer fraction) (undiluted) (Sigma-Aldrich A/S)	÷	÷	NT

+, Positive; ÷, negative; NT, not tested; po, per os (by mouth).

*Results of the SPTs were considered positive when wheal reactions at least 3 mm larger than that elicited by the saline control.

†Results of the direct HR tests were considered positive when introduction induced more than 5 ng of HR per milliliter of blood.

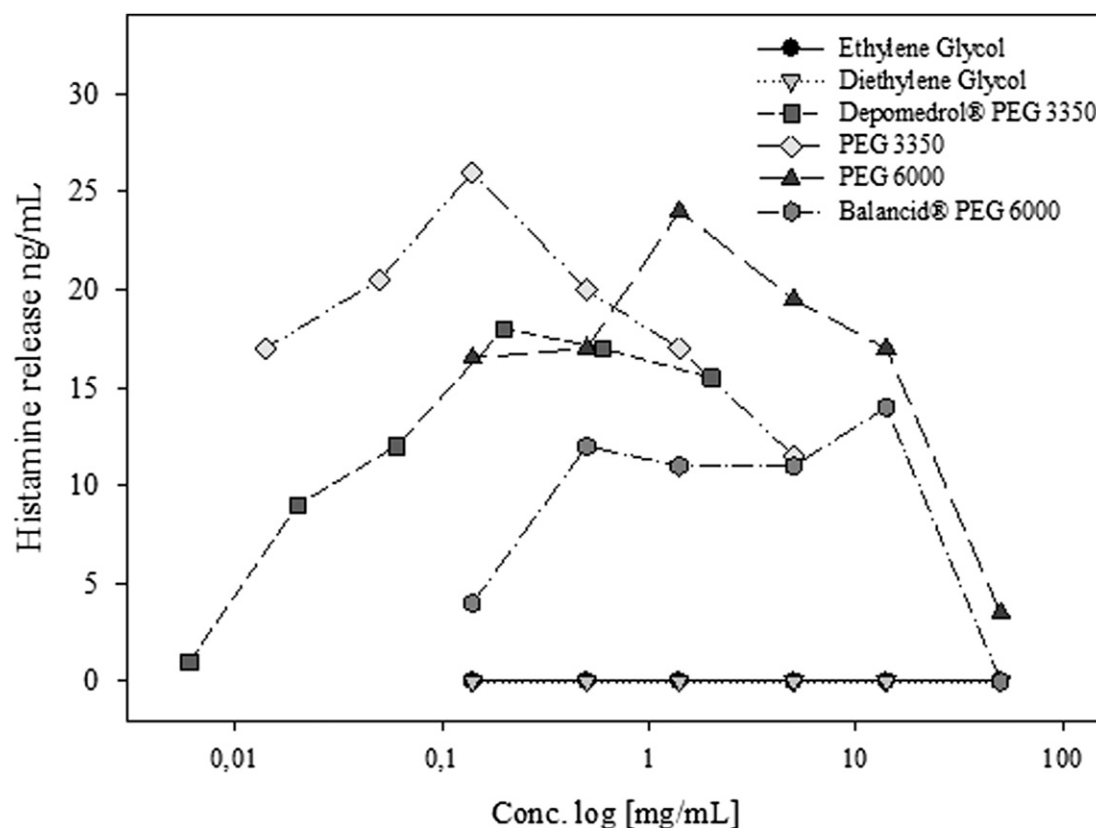


FIG 1. Direct basophil HR test in response to PEG-containing products, ethylene glycol, and diethylene glycol.

Steroid-based products not containing PEG were negative in SPT, the HR test, and provocation, ruling out allergy to steroids. Alternately, SPTs with PEG-containing compounds as well as PEG 3350 and 6000 solutions were positive (Table I). In HR tests, Depo-Medrol, Balacid Novum, PEG 3350, and PEG 6000 induced specific HR from the patient's basophils down to concentrations of 0.02, 0.05, 0.014, and 0.014 mg/mL, respectively. At the lowest concentration (0.014 mg/mL), PEG 3350 and 6000 were still able to induce a substantial HR (Fig 1). Passive sensitization of IgE-stripped donor basophils with patient serum and subsequent challenge with Depo-Medrol and PEG 6000 also showed positive HR in the range of 5 to 50 mg/mL. Control experiments using IgE-stripped basophils incubated with (1) PEG and buffer alone and (2) serum from a nonallergic donor showed no HR, indicating that PEG had no direct, antibody-independent properties and that activation of patient basophils was a PEG-IgE specific reaction. In further demonstration of an IgE-mediated mechanism, patient serum incubated with omalizumab (IgE-blocking antibodies) prior to passive HR tests abolished PEG-mediated HR.

Interestingly, the monomer and dimer fractions of PEG yielded negative SPT and HR test results. In a basophil HR inhibition study, PEG 3350- and 6000-induced HR was abolished by preincubation with the monomer or dimer. This inhibition appeared to be antigen specific, as anti-IgE-induced HR remained unchanged after preincubation with the monomer and dimer (25 and 21 ng histamine/mL, respectively).

These results, in combination with those of the passive sensitization experiment, strongly indicate that serum factors in the patient's blood, possibly IgE antibodies, may bind monovalent ethylene glycol. However, only repetitive presentation of this structure in the form of a polymer chain induces a biological response as demonstrated by a positive SPT and HR test result to PEGs.

The patient's anamnesis, clinical symptoms, and positive SPT results for PEG 3350, PEG 6000, Depo-Medrol, Balacid, and other PEG-containing products point to PEG allergy. Also, positive direct and passive HR tests, as well as the successful inhibition of PEG-induced basophil HR by monomer and dimer fractions of PEG and omalizumab, indicate an IgE-mediated mechanism. Nonetheless, in the absence of a commercially available specific IgE assay for PEG, the mechanism can only be limited to an unidentified serum factor.

To our knowledge, this is the first time an IgE-mediated crosslinking mechanism has been made plausible by inhibition studies using monovalent haptens. We present a unique case of allergy to PEGs of varying molecular weights and exposure routes, with responses provoked by intramuscular (Depo-Medrol), per oral (Balacid), and possibly, intradermal administration (via tattooing). We recommend testing patients for PEG allergy in instances of repeated, idiopathic reactions to PEG-containing substances. With increasing use of PEGs in both household and pharmaceutical products, as well as drug-delivery technology,² an increase in the incidence of allergy to these polymers may be expected. For patients with PEG allergy, avoiding

PEGs is made difficult due to the lack of a standardized nomenclature and clear product labeling.

Emily Cathrine Wenande, BSc^a
Per Stahl Skov, MD, DMSc^{a,b}
Holger Mosbech, MD, DMSc^a
Lars K. Poulsen, DMSc^a
Lene H. Garvey, MD, PhD^a

From ^athe Allergy Clinic, Gentofte University Hospital, Copenhagen, Denmark, and ^bRefLab, Copenhagen, Denmark. E-mail: lene.heise.garvey@regionh.dk.

Funding for the study was exclusively from departmental/institutional sources.

Disclosure of potential conflict of interest: P. S. Skov has consultant arrangements with RefLab Aps, Merck Sharp & Dohme, and GlaxoSmithKline and has provided expert testimony for the Danish Supreme Court. L. K. Poulsen has consultant arrangements with Danish Technical University and Novozymes A/S; has provided expert testimony for Syngenta; has received grants from the European Commission and the National Institutes of Health; has received payment for lectures from ALK-Abelló and Leo Pharma; and has received travel expenses from the European Academy of Allergy and Clinical Immunology. L. H. Garvey is on the adjudication committee and advisory board for, has consultant arrangements with, and has received payment for lectures from Merck. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Fruijtier-Polloth C. Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products. *Toxicology* 2005;214:1-38.
2. Knop K, Hoogenboom R, Fischer D, Schubert US. Poly(ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. *Angew Chem Int Ed* 2010;49:6288-308.
3. Shah S, Prematta T, Adkinson NF, Ishmael FT. Hypersensitivity to polyethylene glycols. *J Clin Pharmacol* 2012;XX:1-4.
4. Savitz JA, Durning SJ. A rare case of anaphylaxis to bowel prep: a case report and review of the literature. *Mil Med* 2011;176:944-5.
5. Hyry H, Vuorio A, Varjonen E, Skytta J, Mäkinen-Kiljunen S. Two cases of anaphylaxis to macrogol 6000 after ingestion of drug tablets. *Allergy* 2006;61:102.
6. Anton Girones M, Roan Roan J, de la Hoz B, Sanchez Cano M. Immediate allergic reactions by polyethylene glycol 4000: two cases. *Allergol Immunopathol (Madr)* 2008;36:110-2.
7. Dewachter P, Mouton-Faivre C. Anaphylaxis to macrogol 4000 after a parenteral corticoid injection. *Allergy* 2005;60:705-6.
8. Sohy C, Vandenplas O, Sibille Y. Usefulness of oral macrogol challenge in anaphylaxis after intra-articular injection of corticosteroid preparation. *Allergy* 2008;63:478-9.
9. Garvey LH, Kroigaard M, Poulsen LK, Skov PS, Mosbech H, Venemalm L, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007;120:409-15.

<http://dx.doi.org/10.1016/j.jaci.2012.09.037>