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Hypersensitivity to Polyethylene Glycols

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Polyethylene glycols (PEGs) are nonionic hydrophilic polymers of ethylene oxide ($\text{HO-CH}_2\text{-(CH}_2\text{-O-CH}_2\text{)}_n\text{-CH}_2\text{-OH}$) that are used extensively in the cosmetic and pharmaceutical industry as surfactants, dispersing agents, bases for ointments, and excipients in a wide variety of substances and medications.¹ Ranging in molecular weights between 200 to 20 000 g/mol, they are characterized by different physical properties (ie, viscosity), and different products may contain PEG polymers of different lengths.¹ PEG with a molecular mass of 3350 g/mol (PEG-3350) is widely used as an osmotic laxative, due to its lack of absorption from the GI tract.¹ PEG polymers can also be covalently linked to proteins and other molecules to decrease toxicity and increase half-life. In part, these effects stem from their immunologically inert characteristics, and PEG molecules are thought to suppress nonspecific interactions and avoid activation of the immune system.¹

PEGs are believed to be chemically inert and are thus believed to be safe products. However, there are emerging reports of delayed and immediate hypersensitivity reactions to PEG-containing substances, suggesting that they have unrecognized allergenic potential. We report a case of a patient with immediate hypersensitivity to PEG and review the literature on PEG allergy. These findings and their implications are discussed herein.

Case Presentation

A 52-year-old white man with a medical history significant for ulcerative colitis presented for an allergy evaluation after developing an adverse reaction to PEG. The patient reported ingestion of approximately 3 oz of PEG-3350 in preparation for a colonoscopy and within minutes experienced flushing, diffuse hives, shortness of breath, tachycardia, lightheadedness, and then a brief loss of consciousness. Emergency services were contacted, and the patient was noted to have wheezing, hypotension, and tachycardia. Administration of epinephrine promptly restored blood pressure and resolved the wheezing, and

the cutaneous symptoms disappeared within an hour. This was the first time that the patient received PEG-3350 as a laxative, and he previously had bowel preps using non-PEG-containing enemas.

On further questioning, the patient reported several other instances of immediate reactions prior to this episode that he initially thought were coincidental but in retrospect all temporally related to PEG exposure. He developed a pruritic maculopapular rash on his forearms that occurred within a few minutes of applying a PEG-containing sunscreen to those areas. The patient was also noted to have swelling of the lips after brushing his teeth with toothpaste containing PEG. Use of non-PEG-containing toothpastes has not resulted in any symptoms. He developed generalized hives after ingestion of metronidazole, 500 mg, used to treat a *Clostridium difficile* colitis. Suspecting that an excipient might have been the trigger for his symptoms, he was able to obtain a metronidazole suspension without PEG, which was tolerated without difficulty. He reported an episode of pruritus, dyspnea, and urticaria within a few minutes of taking a 220-mg naproxen tablet that contained PEG as an excipient. He self-administered epinephrine, and symptoms improved. He has since tolerated naproxen and other nonsteroidal anti-inflammatory drugs in preparations without PEG. He has never had episodes of urticaria, angioedema, respiratory, or other related symptoms outside of PEG exposure and has no reactions with specific avoidance of PEG.

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Table 1. Skin testing to PEG.

Reagent Tested	0.02 mM ^a (PP)	0.2 mM (PP)	2 mM (PP)	20 mM (PP)	0.2 mM (ID)
PEG-200	0 (0)	0 (0)	0 (0)	3/4 (0)	5/20 (4/16)
PEG-1000	0 (0)	0 (0)	0 (0)	3/3 (0)	5/20 (5/17)
PEG-3350	0 (0)	2/3 (0)	3/4 (0)	6/20 (0)	
PEG-9000	5/25 (0)				
Histamine	5/14 (5/11)				
Saline	0 (0)				

Note: Negative control subject in parentheses. Positive skin test results reported in size of wheal/flare (mm).

Abbreviations: PEG, polyethylene glycol; PP, prick-puncture testing; ID, intradermal testing.

^aDilutions of PEG polymer tested, in 20 mM phosphate-buffered saline.

His medical history was otherwise unremarkable. He had no history of atopic disease, and he denied symptoms of asthma, allergic rhinitis, atopic dermatitis, and food allergy. He had no history of adverse reactions to other medications. His family history was significant for heart disease in his parents, and environmental history was noncontributory. His social history was significant for cigarette use and occasional alcohol use. Review of systems was otherwise negative. His physical exam was unremarkable.

Lab and Diagnostic Data

PEG-200, 1000, 3350, and 9000 (obtained from Sigma-Aldrich) were dissolved in sterile 20 mM phosphate buffered saline pH 7.4 (PBS) to a concentration of 20 mM (concentration of PEG-3350 used for the colonoscopy preparation). Serial dilutions were performed using PBS, and all solutions were sterile filtered with a 0.2- μ syringe filter (Fisher Scientific) prior to skin testing. Skin prick testing was performed with various sizes of PEG polymers of different dilutions (1:1000, 1:100, 1:10, full concentration), histamine (10 mg/mL, positive control), and PBS (negative control) on the patient and a negative control subject. As shown in Table 1, the patient had positive skin prick tests to PEG-9000 (at a dilution of 1:1000), PEG-3350 (full concentration), and equivocal results to PEG-200 and PEG-1000. His reactions to the positive and negative controls were appropriate. The negative control subject had similar positive and negative controls but did not react to any of the PEG polymers tested by skin prick. Intradermal testing was performed with the 1:100 dilutions of PEG-200 and PEG-1000, but both subjects immediately developed burning and irritation at the site of administration, and this was thought to be an irritant effect.

Discussion and Literature Review

We present a case of IgE-mediated hypersensitivity to PEG and describe a protocol for skin testing to PEG

polymers. This case and multiple other studies suggest that PEG has the potential to induce both delayed and immediate hypersensitivity reactions. The implications of PEG hypersensitivity are discussed herein.

PEG polymers are considered to be immunologically inert and are widely used in many products.¹ In fact, covalent attachment of PEG to drugs has been a strategy to decrease immunogenicity and toxicity.¹ However, immune reactions to PEG are becoming more evident, and there are multiple reports of immediate and delayed hypersensitivity reactions (Table 2). Several studies have evaluated contact sensitivities to PEG and confirmed the role of these agents by patch testing.²⁻⁸ Bajaj et al performed patch testing on PEG of various sizes (400-6000) in patients with a history of contact dermatitis to various topical ointments and medications and demonstrated sensitivity in 8 of 120 patients.² Similarly, Braun found that 4 of 92 patients with contact dermatitis of unknown etiology were patch-test positive to PEG-300. Furacin (0.2% nitrofurazone with PEG), a topical ointment for burn treatment, is prepared in a base of PEG molecules of varying molecular weights and was noted to cause contact dermatitis reactions in multiple patients.^{3-5,8} Testing by Stenveld et al demonstrated a delayed hypersensitivity reaction to Betadine, a PEG 300 and 400 containing solution, and Flammazine, a silver sulphadiazine-containing ointment.⁸ Similarly, Kalavala et al demonstrated a positive reaction to the specific PEG-7 component of a particular sunscreen, while testing to the rest of the components were negative.⁷ These are only a few examples of the several studies that demonstrate a delayed hypersensitivity reaction to varying PEG-containing substances.

Reports of immediate hypersensitivity reactions in contrast are extremely rare. Fisher et al described 2 cases of immediate reactions to PEG 300 and 400 that produced negative patch testing, but rubbing the respecting agents on the patients' forearms produced an urticarial reaction within 15 minutes.⁴ Anton Gironés et al described 2 additional cases of immediate reactions to PEG-4000 and confirmed these by oral challenge.⁹ Interestingly, both

Table 2. Studies demonstrating hypersensitivity reactions to PEG.

Article	Reaction	No. of patients	Implicated agent	Test results
Bajaj et al ²	Delayed	120	Topical ointments and medications	8 patients patch-test positive to PEG ranging in size from 400-6000
Braun ³	Delayed	92	Unknown causes of contact dermatitis	12 patients patch-test positive to PEG-300
Fisher ⁴	Immediate	2	PEG-300 (in ear drops with 20% benzocaine, 0.1% benzethonium chloride, 1% glycerine) PEG-400 (in topical cotrimazole and tolnaftate)	Urticaria after PEG was rubbed onto skin
Anton Gironés et al ⁹	Immediate	2	PEG-4000	Skin prick test, intradermal test, and oral challenge
Geleijnse et al ¹⁰	Immediate	7	PEG-4000 in sulphur hexafluoride contrast	None
Pérez-Pérez et al ²⁰	Immediate	1	Polysorbate-80 in adalimumab and ustekinumab	Skin prick test

Abbreviation: PEG, polyethylene glycol.

patients had negative skin prick testing to PEG-4000, and after a positive challenge, the authors then performed intradermal testing, which was positive.⁹ Other reports have suggested systemic reactions to PEG. In Europe, 7 cases of anaphylaxis to the PEG-containing intravenous contrast agent sulphur hexafluoride have been described, while none of these reactions have been reported in similar non-PEG-containing agents.¹⁰ While PEG was implicated, diagnostic testing was not performed in these cases.

Our patient described immediate hypersensitivity reactions to a variety of PEG-containing polymers. As PEG polymers are multivalent and potentially large enough to illicit an immune response without haptena-tion, they fit the criteria for complete antigens. We thus postulated that larger PEG polymers would be more immunogenic and performed skin testing using a range of sizes from 200 to 9000 Da. As expected, the skin test sensitivity correlated with polymer size, and skin prick tests were positive to a 1:1000 dilution of PEG-9000 and the full strength of PEG-3350. Thus, skin prick testing to larger PEG polymers, such as PEG-9000 and PEG-3350, may be a sensitive method to detect IgE-mediated PEG allergy. Skin prick tests to PEG-1000 and PEG-200 were more ambiguous, with small wheals that appeared after 45 minutes. Both of these agents at a dilution of 1:100 were irritating to the skin of the patient and the negative control subject on intradermal testing.

The mechanism by which development of PEG allergy occurs is not entirely clear. It has been demonstrated that naturally occurring PEG antibodies are present in normal subjects.¹¹ Furthermore, subcutaneous injection of PEG-modified ragweed and honeybee venom led to development of IgM to PEG in 50% of treated patients within 1 year.¹¹ However, many of these patients lost the antibody after 2 years, and overall the IgM response was found to be weak and not clinically significant. Given our patient's history of ulcerative colitis, he may have been especially prone to the development of PEG allergy. In inflammatory bowel disease, there is a loss of mucosal integrity that can promote the systemic absorption of

PEG.¹² In addition, ulcerative colitis is characterized by a Th2 inflammatory process, and the production of cytokines such as IL-13 favors antibody isotype switching toward IgE.¹³ Thus, the chronic inflammatory state may have uniquely predisposed the patient to development of hypersensitivity to the agent. At the time of the reaction, the patient's disease was in remission, and he was not on any immunosuppressive agents. However, he had been previously exposed to PEG as an excipient in mesalamine during bouts of gastrointestinal inflammation, and this exposure (particularly under these conditions) could have served as a sensitizing event. The immunomodulatory nature of this medication also raises the question of whether immunosuppressive agents in general may increase the propensity for development of hypersensitivity reactions, by disrupting normal mechanisms of immune regulation.

The overall scope of reactions to PEG is unknown. Allergists often evaluate numerous cases where a rash or symptoms consistent with immediate hypersensitivity reactions occur and there is no attributable cause. In addition, patients may develop symptoms secondary to excipients or inactive ingredients in medications. This is an important aspect that is often overlooked when evaluating medication reactions. A common reaction to an excipient could explain hypersensitivity to multiple chemically unrelated drugs.¹⁴⁻¹⁸ It is especially crucial to consider this in the multiple drug allergy patient population, where patient-specific idiosyncrasy may be blamed without a thorough consideration of excipients. Excipients and PEG in particular should also be considered in cases of reactions to injectable biologic agents, where hypersensitivity reactions are common. These immunomodulators frequently produce immunologic reactions, which are often nonspecific in nature.¹⁹ Recently, Pérez-Pérez et al described a patient that developed generalized hives after receiving adalimumab and ustekinumab, with a subsequent positive skin prick test to polysorbate 80, a PEG-containing polymer present in both agents.²⁰ The extent and role of these agents in reactions secondary to immunomodulators is not known but could be significant. Their

presence in monoclonal antibodies such as omalizumab raises the question of whether they might play a role in adverse reactions associated with these agents. The ability to perform skin testing to PEG and other polymers could prove to be very useful. These cases highlight the importance of thoroughly reviewing the chemical components of medications and the consideration of hypersensitivity to PEG and related polymers as inciting agents.

Conclusion

PEG reactions may occur in the form of delayed or immediate hypersensitivity reactions. Patch testing can be a useful means to detect delayed reactions, and we present a protocol for immediate hypersensitivity skin testing. Despite the inert immunologic features of PEG, hypersensitivity to these agents can occur and should be considered in patients with suggestive histories.

Declaration of Conflicting Interests

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