

PEG That Reaction: A Case Series of Allergy to Polyethylene Glycol

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Abstract

Polyethylene glycol (PEG), also known as macrogol, is an excipient in numerous medications, health care products, cosmetics, and foods. It acts as an inert bulking, or stabilizing, agent. Despite its ubiquity, including in 2 of the newly launched vaccines against SARS-CoV-2, awareness of PEG allergy remains low. We present 6 cases of acute hypersensitivity to PEG. Accurate diagnoses in these cases posed a challenge, and although the triggering agents differed, PEG was demonstrated as the common culprit. All cases were female, with a mean age of 36.4 years. Four patients were originally suspected to have nonsteroid anti-inflammatory drug allergy, and 2 had a history of chronic spontaneous urticaria and angioedema. Biphasic allergic reactions featured prominently in this case series. Diagnosis relies on a high index of suspicion leading to a focused clinical history, supported by skin tests with PEG solutions to demonstrate sensitization. This case series highlights important clinical features of this rare, potentially serious, and increasingly recognized excipient allergy.

Keywords

allergy, anaphylaxis, drug allergy, excipient, macrogol, PEG, polyethylene glycol

Polyethylene glycol (PEG), also known as macrogol or E1521, is a commonly used bulking and stabilizing agent. It is an excipient in a wide variety of medications and also encountered in cosmetics and processed foods. Notably, both Pfizer BioNTech and Moderna mRNA vaccines against SARS-CoV-2, which are being internationally deployed to combat the current pandemic, contain polyethylene glycol. Allergy to PEG is rare but is increasingly recognized and can be severe. We present a case series to highlight features of this unusual excipient allergy. A high index of suspicion with early referral for expert diagnostic workup is required to implement appropriate risk management strategies.

The incident case experienced anaphylaxis after intramuscular Depo-Provera administered by her general practitioner. She developed rapid-onset sneezing, rhinorrhea, urticaria, profound hypotension, and chest tightness. She was managed with 2 doses of intramuscular adrenaline, steroids, and nebulized salbutamol. Symptoms improved; however, 6 hours following initial treatment she experienced further urticaria. The patient had recently tolerated similar progesterone in the oral contraceptive pill. Allergy to an excipient ingredient was suspected. The specific intramuscular formulation contained PEG-3350 (Table 1). Skin-prick testing (SPT) was positive and avoidance advised.

The second patient experienced acute urticaria and angioedema following concomitant ibuprofen and esomeprazole ingestion. Nonsteroidal anti-inflammatory drug (NSAID) sensitivity was initially suspected (Table 1). While awaiting further investigation, she devel-

oped urticaria, angioedema, and hypotension following minimal ingestion of the PEG-containing osmotic laxative Movi-Prep. Symptoms settled with steroids and antihistamine; however, she experienced further urticaria 6 hours later. In addition, the patient described contact urticaria with certain cosmetics. PEG was suspected as a common trigger, and SPT was supportive (Table 1).

Case 3 had urticaria and syncope within minutes of effervescent vitamin C and separately developed urticaria, angioedema, and throat tightness with difficulty swallowing after the osmotic laxative Klean-Prep. She gave a history of urticaria associated with Vimovo (esomeprazole and naproxen) and similar symptoms during a dental procedure (Table 1). All identified agents contained high-molecular-weight (HMW)-PEG (Table 1). Unfortunately, SPT was inconclusive because of dermatographism (negative

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Table 1. Patient Case Summary With Triggering Agents and Associated PEG Compounds, Allergic Symptoms Experienced, Outcome of Skin Prick Testing, and Results of Supervised Provocation Challenges Detailed for Each Patient

Case	Allergic Disease	Trigger	Symptoms	Negative Provocation Challenge	Positive Investigation
Case 1 Female, 35 years	None	Depo-Provera: medroxyprogesterone PEG-3350	Sneezing, ocular irritation, rhinorrhea, urticaria, hypotension, chest tightness, respiratory compromise. Biphasic urticaria.	None	SPT PEG-3350: positive, 7 x 7 mm
Case 2 Female, 25 years	None	Nexium: esomeprazole "Macrogols" MoviPrep: osmotic laxative PEG-3350 Cosmetics: PEG-100	Urticaria, angioedema, Respiratory compromise. Pruritus, urticaria, angioedema, hypotension, swelling of hands and feet. Biphasic urticaria. Contact urticaria.	Celebrex: Celecoxib PEG-free "Teva": pantoprazole PEG-free	SPT PEG-3350: positive, 10 x 11 mm
Case 3 Female, 40 years	None	Effervescent vitamin C: HMW-PEG Klean Prep: osmotic laxative PEG-3350. Vimovo: esomeprazole, naproxen. PEG-8000. EMLA topical anesthetic: lidocaine, prilocaine. HMW-PEG.	Urticaria, syncope. Urticaria, angioedema. Urticaria, presyncopal. Generalized pruritus.	Cerazette: desogestrel PEG-400 "Teva": pantoprazole PEG-free	SPT PEG-400, 3350: Inconclusive because of dermographism. Movicol challenge, PEG-3350: positive
Case 4 Female, 44 years	None	Klean Prep: osmotic laxative, PEG-3350. Phosphate Sandoz: effervescent phosphate, PEG-4000. Cosmetics: LMW- and HMW-PEG.	Perioral paresthesia, angioedema, dyspnea, stridor, visual disturbance, syncope. Angioedema, dyspnea, presyncope. Urticaria	None	SPT PEG-3350: positive
Case 5 Female, 36 years	CSUA	Motilium Suppository: domperidone, PEG-400 and 1000. Nurofen: ibuprofen, PEG-6000.	Angioedema, paresthesia, throat tightness. Angioedema, paresthesia, throat tightness.	Motilium oral tablet: PEG-free Nurofen syrup: PEG-free	SPT PEG-3350: positive
Case 6 Female, 38 years	CSUA Physical urticaria	Betadine: wound dressing, povidone-iodine, PEG-400, 6000. Voltorol Oral: diclofenac PEG-8000. Diclofenac IM: HMW-PEG. Shaving foam: LMW- and HMW-PEG. Cosmetics: LMW- and HMW-PEG.	Urticaria, presyncopal. Urticaria. Urticaria, angioedema, respiratory distress, hypotension. Contact urticaria.	Celebrex: Celecoxib PEG-free. Ibuprofen tablet: PEG-free	SPT PEG-3350: 10 x 10 mm

control inciting a wheal). A provocation challenge to HMW-PEG (Movicol) was objectively positive. The patient has remained completely symptom-free with a PEG avoidance strategy. She has tolerated challenges with PEG-free medications.

Anaphylaxis to Klean-Prep was also a presenting feature of the fourth case. A PEG-3350 allergy was suspected and avoidance advised until formal review at an allergy clinic. In the following months, while awaiting assessment and as a hospital inpatient for an unrelated

condition, she had a second anaphylaxis within minutes of taking a PEG-containing effervescent phosphate replacement preparation. SPT was subsequently positive to PEG-3350, which has been avoided since.

The fifth patient was referred for assessment of multiple allergic drug reactions, on a background of chronic spontaneous urticaria and angioedema (CSUA). The first episode occurred within minutes of a Motilium suppository and was managed with intramuscular adrenaline, hydrocortisone, chlorphenamine, and fluid resuscitation. The second episode was precipitated by oral ibuprofen, again requiring adrenaline. PEG was considered a likely trigger, SPT was supportive. The patient subsequently tolerated PEG-free domperidone and ibuprofen (Table 1).

The final case similarly had multiple adverse drug reactions, including anaphylaxis, on a background of CSUA. The initial allergic episode occurred following a Betadine dressing to a wound. She had systemic symptoms with oral and intramuscular diclofenac, oral Solpadeine (paracetamol and codeine), and contact urticaria with various cosmetics (Table 1). The patient subsequently tolerated PEG-free forms of NSAIDs and codeine. PEG was suspected as a common inciting agent, SPT was supportive and strict avoidance recommended. After diagnosis, the patient experienced anaphylaxis while shaving with a product containing PEG requiring self-administration of an adrenaline autoinjector.

This case series illustrates the diverse presentations of PEG allergy. Patients experienced an average of 3 allergic episodes before a formal diagnosis consistent with other case series.¹ Reactions were distressing for patients and objectively severe. Media reports of a case of fatal anaphylaxis in a patient with an established diagnosis of PEG allergy highlight the significance of this emerging problem.² The true incidence of PEG allergy is difficult to determine and may be underestimated.³

It is hypothesized that initial PEG-sensitization could be via cutaneous exposure from cosmetics and hygiene products or absorption of low-molecular-weight (LMW)-PEG in pharmaceuticals.³ The role of LMW-PEG exposure prior to hypersensitivity has not been explored and may merit investigation. A female predominance was noted in our case series, but has not been universally observed.^{1,4} Overall, the literature reports equal incidence between sexes. Interestingly, more recent case reports demonstrate a younger median age of diagnosis compared with older publications.^{1,5} This is likely multifactorial and may be influenced by improved awareness of drug, and specifically PEG allergy, improved access to specialist allergy services, and potentially earlier or greater opportunity for sensitization. This is something that can only be speculated on because of limited clinical data.

Four of the 6 cases were suspected to have an NSAID allergy that was subsequently ruled out with negative provocation tests (Table 1). This emphasizes the prevalence of understandable misdiagnosis and unnecessary drug restrictions in this cohort. A review published in 2016 identified 37 cases labeled as “PEG-allergy,” totaling 74 reactions.⁴ More than half were associated with laxatives, also prominent allergens in this series. PEG-3350 has been listed in more than 1000 approved medications.³ Despite this ubiquity, reported incidence of hypersensitivity appears low. However we demonstrate that reactions can be severe and are diagnostically challenging.

NSAIDs are one of the most common inducers of drug-related hypersensitivity reactions.⁶ PEG sensitivity does not need to be considered in all NSAID-related reactions. However, there are features that can be divined from an allergy history that offer pointers toward the need for PEG sensitization assessment. Patients with multiple episodes of “unexplained” anaphylaxis or tolerance of individual brands of the same drug merit closer investigation. Reactions to laxatives or bowel preparations, “depo” medications, and mucosal absorption from lubricants, gels, and dressings are red flags that should have PEG hypersensitivity in the differential. Bruusgaard-Mouritsen et al (2021) similarly highlighted analgesics, depo injections, and laxatives as common triggers in their cohort, as well noting antacids and antibiotics as culprits.¹

We recommend that an adrenaline autoinjector be prescribed to those with PEG allergy because of an ongoing risk of accidental exposure. Unfortunately, comprehensive avoidance list cannot be provided, as medical preparations frequently change; thus, awareness is key. We advise patient empowerment with education, supported by step-by-step instructions on how to interrogate summary of product characteristics (SPC) for the variety of terms that indicate a PEG excipient. Patients are advised to engage with pharmacists and inform all health care professionals encountered of the disorder. In addition they should wear alert jewelry and only take a medication when they and their health care professional are satisfied that it does not contain PEG. Effective use of an electronic patient record can assist with communicating this issue, but as with all drug allergy, effective communication among disparate health care providers is a challenge. In addition, the cases presented here suggest a higher rate of biphasic allergic reactions than might be expected.⁷ Based on these observations, we recommend extended monitoring for 12 hours after resolution of symptoms following a PEG-related reaction. Although biphasic symptoms are usually mild, they can be distressing, especially to patients who have had a history of unexplained adverse events.

The identification of PEG allergy is increasing. These cases offer insight into the variety of ways this allergy can present. We report characteristics that flag PEG as a potential trigger and highlight the need for extended observation after resolution of symptoms because of the risk of biphasic reactions. Reports of immediate hypersensitivity in 2 health care workers on the first day of mass COVID-19 vaccination in the United Kingdom are concerning.⁸ It remains unknown if PEG-2000 is involved in these reactions. Leaders in allergy have already engaged with regulatory authorities to highlight PEG as a possible allergen in mRNA vaccines and to support the objective investigation of reported reactions.⁹

PEG allergy is now well known among allergy professionals. However, increased awareness of this allergy among the wider medical community is needed. Early recognition through a thorough clinical history and rapid referral to allergy diagnostic centers is required to confirm the diagnosis and effectively manage this high-risk drug allergy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Data-Sharing Statement

Please contact the corresponding author, Dr Fionnuala Cox, on coxff@tcd.ie, if you wish to request further information on study data.

Author Contributions

F.C. conceived the study and interpreted data. F.C., N.C., and K.K. diagnosed and managed patients. All authors contributed to the writing and approval of the article.

References

1. Bruusgaard-Mouritsen MA, Johansen JD, Garvey LH. Clinical manifestations and impact on daily life of allergy to polyethylene glycol (PEG) in ten patients. *Clin Exp Allergy*. 2021. doi: 10.1111/cea.13822.
2. Roseingrave L. Verdict of medical misadventure in case of fatal allergic reaction. *The Irish Times*. <https://www.irishtimes.com/news/crime-and-law/courts/coroner-scourt/verdict-of-medical-misadventure-in-case-of-fatal-allergic-reaction-1.3324937>. Published January 2, 2021. Accessed January 2, 2021.
3. Stone CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533-1540.e8.
4. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review *Clin Exp Allergy*. 2016;46(7):907-922.
5. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (Anaphylaxis). *J Allergy Clin Immunol Pract*. 2021;9(2):670-675.
6. Blanca-Lopez N, Soriano V, Garcia-Martin E, Canto G, Blanca M. NSAID-induced reactions: classification, prevalence, impact, and management strategies. *J Asthma Allergy*. 2019;12:217-233.
7. Pourmand A, Robinson C, Syed W, Mazer-Amirshahi M. Biphasic anaphylaxis: a review of the literature and implications for emergency management. *Am J Emerg Med*. 2018;36(8):1480-1485.
8. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. Longo DL, ed. *N Engl J Med*. 2020:NEJMra2035343. doi: 10.1056/NEJMra2035343.
9. Update on MHRA decision re: Pfizer COVID-19 Vaccination 30.12.20. *BSACI*. Published December 30, 2020. Accessed January 2, 2021. <https://www.bsaci.org/update-on-mhra-decision-re-pfizer-covid-19-vaccination/>.