Article type: Original article

Title: Allergy to polyethylene glycol has significant impact on daily life

Short running title: Impact on daily life of a diagnosis of PEG allergy

Maria A. Bruusgaard-Mouritsen[1], Jeanne D. Johansen[1], Lene H. Garvey[2,3]

[1]Department of Dermatology and Allergy, National Allergy Research Centre, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark.
[2]Allergy Clinic, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Hellerup, Denmark
[3]Department of Clinical Medicine, University of Copenhagen, Denmark

Acknowledgements
None

Funding
A grant from the Danish Environmental Protection Agency to The National Allergy Research Centre.

Conflicts of interest
None

Corresponding author
Maria Anna Bruusgaard-Mouritsen
National Allergy Research Centre
Department of Dermatology and Allergy
Herlev and Gentofte Hospital, University of Copenhagen
Gentofte Hospitalsvej 20A, 2nd floor
2900 Hellerup, Denmark
E-mail: maria.anna.bruusgaard-mouritsen@regionh.dk
Telephone: +4538677303

Keywords: Anaphylaxis, drug allergy, macrogol, PEG, polyethylene glycol

Wordcount: 2.356

Author contribution:

Maria Anna Bruusgaard-Mouritsen: Conzeptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing-original draft, Writing-reviews & editing

Jeanne Duus Johansen: Conzeptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing-reviews & editing

Lene Heise Garvey: Conzeptualization, Methodology, Project administration, Resources, Supervision**,** Writing-reviews & editing

Abstract

Introduction: Polyethylene glycols (PEGs) are widely used as excipients in drugs, cosmetics and household products. Immediate-type allergy to PEGs including anaphylaxis are reported with low but increasing frequency. Low awareness of the allergenic potential of PEGs among consumers, manufacturers and doctors leads to under-diagnosis and under-reporting of PEG allergy, putting patients at risk of repeated severe reactions. The aims of this study were to investigate clinical manifestations, time to diagnosis and impact of a PEG allergy diagnosis on daily life of patients.

Method: Ten PEG allergic patients answered a questionnaire about clinical manifestations, causes and impact on daily life of a PEG allergy, scored on a likert scale (0-10) before and after diagnosis.

Results: Eight patients had experienced at least one anaphylactic reaction requiring adrenaline treatment. Anaphylaxis was caused by depot-steroids, antibiotic/analgesic tablets, antacids and laxatives. Seven patients reported repeated reactions before diagnosis (median 3, range 2-6). Median time from first reaction to diagnosis was 20 months (range 2-120). None of the patients experienced severe allergic reactions after the diagnosis. Median likert score of the impact on daily life before diagnosis was 7 compared to 4 after diagnosis.

Conclusion: Daily life of PEG allergic patients is improved after diagnosis. Detailed information about the allergy, an allergy warning card, education in checking labels of new products, continued follow-up and advice from the Allergy Department were reported by patients to be important. Improved awareness about PEG allergy, clear product labelling and a standardized nomenclature is needed to improve care for these patients.

Introduction

Polyethylene glycols (PEGs) or macrogols are widely used as excipients in pharmaceutical, cosmetic and household products. PEGs are added to optimize the properties of a product and are commonly used as tablet surface coatings, pill binders, lubricants, ointment and cream bases as well as in wound dressings, bone cement, dural sealants and in polymer-based drug delivery (PEGylated drugs). They are generally considered to have low toxicity and to be biologically inert. Although allergy to PEGs is rare, immediate-type allergy, often with severe reactions including life-threatening anaphylaxis, has been described with increasing frequency in the past two decades following an increased focus on these "hidden" allergens.[1–4]
PEGs are difficult to avoid due to the widespread use and patients with PEG allergy are at particular risk of re-exposure due to the lack of a standardized nomenclature and insufficient product labeling.[1,2,5]
PEGs are polymers of ethylene oxide. In cosmetic products, PEGs are described by the average number of ethylene oxide units, i.e. PEG 100.[1,2] In pharmaceutical products, PEGs are described by the total molecular weight of the number of ethylene oxide units and the synonym macrogol is often used. As the molecular weight of ethylene oxide is 44 g/mol, macrogol 4400 g/mol is calculated as 100 x 44 = 4400. Consequently, PEG 100 and macrogol 4400 is the same compound but named differently depending on the product. PEG molecular weights range from around 200 to 50,000 g/mol.[1,6]
In addition to being named differently depending on product type, PEGs also have numerous other synonyms.[1]
The non-standardized nomenclature combined with low awareness of the allergenic potential of PEGs among consumers, manufacturers and doctors leads to under-diagnosis and under-reporting of PEG allergy, putting patients at risk of experiencing repeated severe reactions before the diagnosis is made.[1] Patients with PEG allergy may also have cross-reactions to PEGylated drugs and structurally similar polymers, such as polysorbates and poloxamers.[1]
Beside the risk of repeated life-threatening anaphylactic reactions, patients are also at risk of substandard care due to fear of anaphylaxis on introducing new treatments. The impact on patients´ daily life has not been previously investigated and the aim of this study was to investigate clinical manifestations, time to diagnosis and the effect on patients´ daily life in patients with PEG allergy. To our knowledge, this is the largest series of PEG allergic patients reported so far.

Methods

Study population

This was a retrospective questionnaire study of patients diagnosed with PEG allergy at the Allergy Clinic, Department of Dermatology and Allergy at Copenhagen University Hospital Gentofte during a nine-year period from 1. September 2010 to 31. August 2019. A total of twelve patients were diagnosed with PEG allergy in the department between 3 weeks to 8 years prior to the study start. One patient had died making 11 patients eligible for inclusion in the study.

Questionnaire

Between 10. October 2017 and 15. November 2019, 11 patients diagnosed with allergy to PEG were sent a questionnaire by mail (see supplementary material).

It comprised 11 questions about exposure to PEGs, suspected causes, allergic symptoms, and the impact on their daily life scored on a likert scale (0-10) before and after diagnosis, where 0 was no impact on daily life and 10 was severe impact on daily life. Furthermore, the patients were asked what they perceived to be the most important information from the healthcare professionals when diagnosed with PEG allergy.

The study was approved by the regional ethics committee with number H-17021145.

Results

One patient declined participation; thus 10 patients were included (6 men and 4 women). The median age was 35 years (range 18-64 years).

None of the patients had heard about PEG allergy before diagnosis, although one patient had a suspicion towards excipients after anaphylaxis to two different products. Nine patients reported either knowing or suspecting which products had caused their reactions (Table 1), and eight patients reported more than one product causing reactions. Healthcare products, but also cosmetic products and hygiene products (razors, toothpaste and dental floss) were reported as possible causes.

Table 1. Products suspected by patients to cause allergic reactions.

Products	Number of patients (n=10)
Tablets (analgesics, antacids, antibiotic tablets)	7
Steroid injection	6
Shaving products (razors and shaving gel)	5
Creme/ointment	4
Mouth hygiene products (toothpaste, mouth wash, dental floss)	3
Hand soap	2
Laxatives	2
Hair products (shampoo, hair colouring)	2
Make-up and make-up remover	1
Vaseline used in connection with tattooing	1
Hormone injections during fertility treatment	1
Cough medicine	1
Epoxy used in workplace	1
Cleaning agent	1

Seven patients reported repeated reactions (median 3, range 2-6) before diagnosis. For all patients, median time from first reaction to diagnosis was 20 months (range 2-120 months). All patients experienced immediate hypersensitivity symptoms within 10 minutes of exposure. The most common symptoms were urticaria, itching, redness, general discomfort, angioedema, breathlessness, burning sensation and fainting. Eight patients had experienced at least one episode of anaphylaxis with skin symptoms, combined with respiratory or circulatory compromise, requiring adrenalin treatment before diagnosis. The most severe reaction was a case of perioperative cardiac arrest. Main products confirmed to have caused anaphylaxis are shown in table 2. Three patients were misdiagnosed with penicillin allergy, idiopathic anaphylaxis and chronic idiopathic urticaria, respectively, before the correct diagnosis of PEG allergy.

Table 2. Main PEG-containing products confirmed to have caused anaphylaxis.

Products	Number of patients experiencing anaphylaxis
Analgesic tablets (specific formulations of paracetamol and ibuprofen)	6
Antibiotic tablets (same specific formulation of penicillin)	6
Depot steroid injections (methylprednisolone)	6
Antacids (calcium carbonate-magnesiumhydroxide)	4
Laxatives (macrogol)	3

After the diagnosis was made, four patients reported accidental re-exposure mainly due to cosmetic products (hand soap, shampoo, cream, toothpaste, razors and shaving gel) but also pharmaceutical products (tablets, steroid cream, hormone injections during fertility treatment). All four patients reported itching, and three patients reported angioedema. One patient with preexisting asthma reported breathlessness. Symptom onset was within 0-10 minutes in all patients. None of the patients needed treatment with adrenaline or hospitalization.

Median likert score on impact on daily life before diagnosis (scored retrospectively) was 7 (range 0-10) compared to 4 (range 0-8) after diagnosis. After diagnosis, seven patients still reported limitations to their daily life. Some patients experienced periods of stress and anxiety either before or after diagnosis as a result of the overwhelming fear of a new anaphylactic reaction due to the widespread use of PEG.

All patients were aware of the use of PEGs in pharmaceutical products and potential exposure on contact with the health care sector. Nearly all patients were aware of the use of PEGs in cosmetics and checked for PEGs in cosmetic products before using them. All patients reported informing about their allergy when in contact with hospitals, general practitioners, specialists, dentists and hairdressers.

Four patients had experienced work- or school-related exposure from soap, cream and cleaning products. None of the patients had to quit their job or school.

All patients specified the importance of receiving sufficient information about allergy to PEG when their diagnosis was made. The most valuable information from the patients´ point of view was information on which products contain PEGs as well as how to check if a product contains PEGs, e.g. by reading the package insert and/or the product information on the Danish Medicines Agency homepage. The fact that numerous products contain PEG was also valuable information. The patients additionally emphasized the importance of receiving an allergy warning card, follow-up appointments and the possibility of continued access to advice from a doctor at the Allergy Clinic. Most of the patients have had several contacts to the department asking advice about medications they were prescribed or treatments they needed after the diagnosis was made. Also, in cases of hospital admissions or need for treatment, e.g. surgical procedures, chemotherapy or fertility treatment, advice has been sought by health care personnel treating the patients. Some patients expressed a need for a PEG-containing product database and an online forum or focus group with other patients diagnosed with PEG allergy.

Discussion

We found that allergy to PEG has severe impact on the patients´ daily life with some improvement after diagnosis. However, more than half of the patients continued to experience some limitations to their daily life. Before diagnosis, 80% of the patients had experienced one or more episodes of anaphylaxis requiring adrenalin treatment. This is consistent with the findings in a review by Wenande et al., where 76% of identified cases experienced anaphylactic reactions with more than half being caused by laxatives or bowel preparations.[1] In this study, all patients´ initial allergic reactions were caused by exposure to pharmaceuticals. The main products causing anaphylaxis were depot-steroid injections, analgesic tablets, antacids, antibiotic tablets and laxatives. Several other studies and case reports have also described initial allergic reactions to PEGs caused by exposure to pharmaceuticals, especially laxatives and depot-steroid injections.[1,8–11]

Due to widespread use of PEG in over-the-counter medication such as analgesics, antibiotics, antacids and laxatives, most patients in our cohort had several allergic reactions to PEGs before diagnosis. Similar findings have been described in numerous case reports.[2,11–16] The median time to diagnosis was two years, emphasizing the difficulty in making the diagnosis of PEG allergy. A diagnosis of PEG allergy is made by a convincing clinical history of reactions to two or more structurally unrelated PEG-containing products confirmed by a positive skin prick test with PEG in one or more concentrations, e.g. PEG 300, PEG 3000, PEG 6000. Oral provocation and intradermal testing are not routinely recommended due to the risk of inducing severe allergic reactions.[1]

None of the patients in our study were aware of PEGs or PEG allergy until the diagnosis was made during allergy investigations. Importantly, only one of the healthcare professionals who had been treating the patients for their allergic reactions suspected PEG as the culprit. Several patients were misdiagnosed with idiopathic anaphylaxis, urticaria or allergy to the active ingredient in drugs, e.g. penicillin prior to the diagnosis. Other case reports have shown similar cases of patients with misdiagnoses.[12,17]
When PEG allergy is suspected, several actions can be taken in order to help the patient (table 3). In general, investigation, diagnosis and follow-up of patients with allergy to PEGs is challenging due to the lack of standardized test method for PEGs and the need for special expertise and comprehensive follow-up by an allergist with specific knowledge about PEG allergy.[12] Most patients in this cohort have had several subsequent contacts to the Allergy Department asking advice about medication they were prescribed. In addition, on many occasions health care professionals have sought advice on how to avoid exposure to PEG during various medical treatments or surgical procedures.

Table 3. PEG allergy recommendations.

1	Suspect PEG allergy in patients with allergic reactions to ≥ 2 structurally different drugs.
2	Investigate and diagnose patients with skin prick testing containing a standardized panel of PEGs.[1]
3	Provide patients with detailed information about their allergy.
4	Educate patients in manually checking labels for cosmetic products and pharmaceutical drugs.
5	Provide patients with an allergy warning card, follow-up appointments and continued access to advice from an allergist with special knowledge about PEG allergy.
6	Take initiatives to address the insufficient product labelling and the need for a standardized nomenclature in cosmetic and pharmaceutical products.

Two examples of special challenges regarding medical treatment among PEG allergic patients in our department have been cancer treatment and fertility treatment. A former patient with PEG allergy was initially refused treatment of his cancer with chemotherapy by the attending physicians, who had no knowledge about PEG allergy and considered the risk of allergic reactions to be too high. After intervention by an allergist from our department, the planned treatments were reviewed for PEG content and relevant treatment without PEG could be given uneventfully. The patient later had an urticarial reaction to a bandage where PEG was used on the surface to increase absorption. A special challenge in cancer treatment is that chemotherapy drugs are often PEGylated. PEGylation is the conjugation of PEGs to drugs, leading to prolonged half-life in plasma and less immunogenicity without compromising the clinical efficacy.[18,19]
Another patient was undergoing fertility treatment using subcutaneous injections. Prior starting the treatment, our department was asked to check for PEG content in numerous drugs potentially needed during treatment. Despite our best efforts, the patient developed rapid onset urticaria during fertility treatment probably caused by a reaction to a structurally related polymer and had to stop the treatment before time. These two examples show that treating patients with PEG allergy can be challenging, complicated and demanding on resources.

When diagnosed with PEG allergy, the patients are advised to inform the local pharmacist to get assistance in ensuring that any medicine or over-the-counter product is PEG-free. As the PEG content may vary in different formulations of the same drug, and even in different doses of the same formulation, each individual drug needs to be checked for PEG. Also, new parallel imports of drugs appear frequently for common drugs such as paracetamol and the excipients may vary. For those reasons it is not possible to compile a list of "safe" PEG-free drugs even though the patients requested it, as it may give a false sense of security. Thus, patients are encouraged to identify their own safe products for over-the-counter or prescription medicine and to bring their own medication, e.g. pain killers in case of hospitalization. Some drug groups almost all contain PEG and in Denmark it is difficult to find proton pump inhibitors or contraceptive pills without PEGs. Importantly, most antihistamines contain PEGs which have implications for treatment of allergic symptoms.[7]

Some patients suggested that an online forum or focus group with other patients diagnosed with PEG allergy could be useful for exchanging experiences. Currently, a few patient initiated online forums exist with PEG

allergic patients helping and supporting each other. Investigations with these types of patient interventions have not been described in the literature to date.

Almost half of the patients in this cohort experienced accidental re-exposure and reactions to PEG-containing products despite great efforts to avoid it. Re-exposures were mainly caused by everyday cosmetic products used on the skin such as soap, shampoo and razors and none of the patients experienced serious reactions to this type of re-exposure. The most popular razors on the market have a gel pad containing PEGs. In several of our patients, using these led to instant localized redness, itching and/or urticaria. Shaving using a razor with a PEG-containing gel pad may be an important entry source through microlacerations in the skin, which could play a role in sensitization to PEGs.

To the best of our knowledge, this is the largest cohort of patients with PEG allergy reported so far. However, a cohort consisting of only ten patients is also a limitation to the study. The patients have been included with varying frequencies up to eight years from first symptoms and diagnoses until answering the questionnaire and some patients may have recall bias. Although only a limited number of patients with PEG allergy have been diagnosed until now, the frequency is expected to rise with increased awareness of this allergy.[1,19]

In conclusion, this study shows that the diagnosis of PEG allergy is often delayed, leading to repeated, severe allergic reactions significantly affecting daily life of patients. PEGs are difficult to avoid due to the widespread use causing a high risk of inadvertent re-exposure. However, once the diagnosis has been made, several actions of importance to the PEG allergic patient can be taken to help them avoid potentially life-threatening re-exposure to PEG-containing products, thereby improving the daily life for these patients.

Referencer

1. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46(7):907-922.
2. Jover Cerdá V, Rodríguez Pacheco R, Doménech Witek J, Marco de la Calle FM, de la Sen Fernández ML. Immediate hypersensitivity to polyethylene glycols in unrelated products: when standardization in the nomenclature of the components of drugs, cosmetics, and food becomes necessary. *Allergy Asthma Clin Immunol*. 2019;15(1):9.
3. Antolin-Amerigo D, Sánchez-González MJ, Barbarroja-Escudero J, Rodríguez-Rodríguez M, Álvarez-Perea A, Alvarez-Mon M. Allergic reaction to polyethylene glycol in a painter. *Occup Med (Lond)*. 2015;65(6):502-504.
4. Calogiuri G, Foti C, Bilo MB, Garvey LH. Macrogols: A Misleading Cause of Drug Hypersensitivity Diagnosis. *Clin Immunol Endocr Metab Drugs*. 2016;4(1).
5. Wenande EC, Skov PS, Mosbech H, Poulsen LK, Garvey LH. Inhibition of polyethylene glycol-induced histamine release by monomeric ethylene and diethylene glycol: a case of probable polyethylene glycol allergy. *J Allergy Clin Immunol*. 2013;131(5):1425-1427.
6. 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 Engl*. 2010;49(36):6288-6308. doi:10.1002/anie.200902672
7. Berndt K, Kuske M, Beissert S, Spornraft-Ragaller P, Bauer A. Non-IgE-dependent hypersensitivity to macrogol 6000. *JDDG - J Ger Soc Dermatology*. 2018;16(4):479-481.
8. Stone CA, Liu Y, Relling M V, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. *J allergy Clin Immunol Pract*. 2019;7(5):1533-1540.e8.
9. Gökay SS, Çelik T, Sari MY, Ekinci F, Yildizdaş RD, Yilmaz HL. Urticaria as a rare side effect of

polyethylene glycol-3350 in a child: Case report. *Acta Clin Croat*. 2018;57(1):187-189.

10. Lee SH, Hwang SH, Park JS, Park HS, Shin YS. Anaphylaxis to polyethylene glycol (Colyte®) in a patient with diverticulitis. *J Korean Med Sci*. 2016;31(10):1662-1663.

11. Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. *Allergy, Asthma Clin Immunol*. 2016;12(1).

12. Brandt N, Garvey LH, Bindslev-Jensen U, Kjaer HF, Bindslev-Jensen C, Mortz CG. Three cases of anaphylaxis following injection of a depot corticosteroid with evidence of IgE sensitization to macrogols rather than the active steroid. *Clin Transl Allergy*. 2017;7:2.

13. Wenande E, Kroigaard M, Mosbech H, Garvey LH. Polyethylene glycols (PEG) and related structures: overlooked allergens in the perioperative setting. *A&A case reports*. 2015;4(5):61-64.

14. Shah S, Prematta T, Adkinson NF, Ishmael FT. Hypersensitivity to polyethylene glycols. *J Clin Pharmacol*. 2013;53(3):352-355.

15. Jakubovic BD, Saperia C, Sussman GL. Anaphylaxis following a transvaginal ultrasound. *Allergy Asthma Clin Immunol*. 2016;12(1):3.

16. Cerdá VJ, Pacheco RR, Witek JD, De La Calle FMM, De La Sen Fernández ML. Immediate hypersensitivity to polyethylene glycols in unrelated products: When standardization in the nomenclature of the components of drugs, cosmetics, and food becomes necessary. *Allergy, Asthma Clin Immunol*. 2019;15(1).

17. Co-Minh HB, Demoly P, Guillot B, Raison-Peyron N. Anaphylactic shock after oral intake and contact urticaria due to polyethylene glycols. *Allergy*. 2007;62(1):92-93.

18. Liu Y, Smith CA, Panetta JC, et al. Antibodies Predict Pegaspargase Allergic Reactions and Failure of Rechallenge. *J Clin Oncol*. 2019;37(23):2051-2061.

19. Sahiner UM, Tolga Yavuz S, Gökce M, et al. Anaphylactic reaction to polyethylene-glycol conjugated-asparaginase: Premedication and desensitization may not be sufficient. *Pediatr Int*. 2013;55(4):531-533.

Supplementary material

Table A1. Questionnaire about PEG allergy

1. Had you heard about allergy to PEGs before your clinical investigation and diagnosis?
Yes; No
2. Did you suspect that you had allergy to PEGs before you had the diagnosis?
Yes; No
3a. Do you know which product caused your allergic reactions to PEGs?
Yes; No
If yes in 3a. Which product caused the allergy?
Tablets; laxatives; suppositories; wound bandages; catheter lubricant/ultrasound gels; medicine through the vein; creme/ointment; hair products; make-up or make-up remover; shaving products; mouth hygiene products (toothpaste, dental floss, mouthwash); other:_____
4. Which symptoms led to clinical investigation?

Itching skin; burning sensation; redness; rash; angioedema; allergic shock; breathing difficulties; feeling unwell; fainting; other:_____
5. Which information about PEG allergy was most important to you?
_____
6a. Have you been exposed to PEGs since the allergy was diagnosed?
Yes; No
6b. How many times?
1; 2; 3; Don't know
6c. When was your last allergic reaction?
_____
6d. If yes in 6a: Which product caused it?
Tablets; laxatives; suppositories; wound bandages; catheter lubricant/ultrasound gel; medicine through the vein; creme/ointment; hair products; make-up or make-up remover; shaving products; mouth hygiene products (toothpaste, dental floss, mouthwash); other:_____
6e. If yes in 6a: Which symptoms did you experience?
Itching skin; burning sensation; redness; rash; angioedema; allergic shock; breathing difficulties; feeling unwell; fainting; other:_____
6f. If yes in 6a: When did you experience the symptoms?
0–10 min; 10–30 min; 30-60 min; more than 60 min
7a. Do you know that PEGs can be used in some cosmetic products?
Yes; No
7b. Do you check for PEGs in a cosmetic product before you use it?
Yes; No
8a. Do you know that PEGs are used at hospitals?
Yes; No
8b. Do you mention your allergy when you are in contact with the healthcare system?
Yes; No
9a. Have you been exposed to PEGs in your current job or in a previous job?
Yes; No
9b. If yes in question 9a: What was your job?
_____
9c. If yes in question 9a: Which product contained PEGs?
_____
9d. If yes in question 9a: Did you have to quit your job?
Yes; No
10. How much impact did the allergy have on your daily life on a scale from 0-10, where 0 is no impact and 10 is severe impact, before and after you were diagnosed?
_____
11a. Does the allergy cause limitations in your everyday life?
Yes; No
11b. If yes in 11a: How does the allergy limit you?
_____

Translated from Danish