Title:

Polyethylene glycol hypersensitivity, patient outcomes in a seven year retrospective study.

Short title:

PEG hypersensitivity: insights and outcomes.

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Abbreviations: HSR (hypersensitivity reactions); IgE (Immunoglobulin E); PEG (polyethylene glycol); SPT (skin prick testing); IDT (intradermal testing); MW (molecular weight), COVID (coronavirus disease); DPT (drug provocation testing).

Abstract:

Background: Immediate IgE-mediated hypersensitivity reactions to polyethylene glycol (PEG) are rare. Our understanding of PEG hypersensitivity reactions is limited. We evaluate the clinical characteristics and investigation outcomes of the largest cohort of PEG allergic patients reported so far.

Method: 44 patients investigated for suspected PEG allergy across four UK tertiary allergy centres between October 2013 and December 2020 were studied. Clinical characteristics, details of index reaction, and approaches to and outcomes of allergy investigations were analysed.

Results: PEG hypersensitivity was confirmed in 42 of 44 cases. Macrogol laxatives were the most common index drugs reported (23%), followed by depo-medroxyprogesterone (19%), oral penicillin V (10%), and depo-methylprednisolone (10%). 61% experienced grade III anaphylaxis. Intradermal testing (IDT) increased the diagnostic sensitivity from 51% to 85%. Five patients experienced systemic reactions during IDT. Of the five patients, two were skin prick test (SPT)-positive to a high molecular weight (MW) PEG. Seven PEG-allergic patients reported tolerance to H1 antihistamines containing PEG. Administration of mRNA COVID-19 (n=5) or AZ COVID-19 vaccines (n=14) was tolerated in 16 patients.

Conclusion: PEG hypersensitivity is an uncommon cause of drug-induced anaphylaxis. Four index drugs accounted for two-thirds of cases and reactions to these drugs should prompt PEG hypersensitivity investigations. PEG IDT increases diagnostic yield. The role of SPT with higher MW PEGs requires further attention. We observed no correlation in PEG dose and concentration between the implicated and tolerated PEG-containing drugs. Further studies are required to understand PEG thresholds and PEG equivalent doses of various administration routes. COVID-19 vaccines were tolerated by all exposed.

Introduction:

Polyethylene glycols (PEGs) are a family of polyether polymers. PEGs possess hydrophilic, non-toxic, odourless, flexible and water-soluble properties1,2. They are used as medical, pharmaceutical, cosmetic and food additives. Due to the vast usage, PEG exposure can occur in various settings, from hospitals to households. 1,2 Further details regarding PEG's structure, utility and nomenclature can be found in Figure E1.

PEG and PEG-ylated products have been associated with immune-mediated adverse reactions including anaphylaxis.3, 4, 5Although rare, cases of immediate hypersensitivity reactions (HSRs) to PEG have been reported as early as 1990 and are being described with increased frequency.4, 6 Owing to the multiple PEG nomenclature synonyms, PEG identification on labelling inspection can be challenging and easily missed, Table E1. It is not uncommon for patients to present with reactions on first exposure to a PEG-containing medication. However, diagnosis is often delayed and after re-exposure and multiple reactions. PEG sensitisation has been suggested to occur percutaneously from use of cosmetic products containing readily absorbed Low Molecular Weight (LMW) PEG.4 Indeed, anti-PEG specific IgEs (sIgEs) have been identified by dual cytometric bead assay in a small number of healthy patients.3

In a small cohort of patients with a clinical history of immediate PEG hypersensitivity, anti-PEG-sIgE, PEG reactivity on skin testing, and PEG-induced basophil activation have been demonstrated. 3, 4, 7 However, to date, there is no international consensus on protocols for investigating and managing PEG hypersensitivity.

Methods:

*Patients*

This multi-centre retrospective study comprised adult patients referred to four UK tertiary allergy centres: Guy’s and St Thomas’ NHS Foundation Trust (London), Cambridge University Hospitals NHS Foundation Trust (Cambridge), Royal Liverpool and Broadgreen University Hospital, NHS Foundation Trust (Liverpool) and Sheffield Teaching Hospitals NHS Foundation Trust (Sheffield).

The medical records of patients investigated for suspected immediate PEG hypersensitivity between October 2013 and December 2020 were reviewed. Our cohort encompassed patients with a high clinician-determined pre-test probability of PEG excipient allergy. Data collected included demographics, past medical history, symptoms of index reaction, index reaction severity using Brown’s severity scale (Table E2)8, index drug and route of administration, interval between testing and index reaction, acute and baseline serum mast cell tryptase results, and outcomes of PEG hypersensitivity investigations.

Ethical approval for this retrospective anonymised study was not required in the United Kingdom. All data collected were obtained purely for clinical reasons, and no patient-identifiable information was available to clinicians who were not part of the clinical care team.

*Allergy work-up*

Patients underwent skin prick (SPT) and, where appropriate, intradermal testing (IDT). Skin test (SPT and IDT) negative patients also underwent drug provocation testing (DPT).

Skin tests were performed with the index drug and/or the index MW PEG. SPT and IDT were considered positive if wheal size or wheal expansion was ≥ 3mm at 15-20 minutes. Sodium chloride 0.9% and histamine dihydrochloride at 10mg/ml were used as negative and positive controls respectively.

*SPT and IDT concentrations*

Across the four centres, PEG3350 or 4000 SPTs were performed using Macrogol Oral Powder (Galen Ltd, UK), Movicol (Norgine Ltd, UK) or Peglax (Casen Recordati, Spain) dissolved in water for injection to give a 100mg/mL (10%) solution. Further 10-fold dilutions in 0.9% sodium chloride were performed to obtain final concentrations ranging from 1:10 (10%) to 1:1,000 (0.1%) for SPT and 1:1,000 (0.1%) to a maximum of 1:100 (1%) for IDT.

Full list of drugs and concentrations/dilutions used for SPT and IDT presented in (Table E3).

In a subgroup of patients, skin tests were not limited to the index MW PEG. Those patients also underwent SPT/IDT to a range of PEG MWs (200 - 20,000 PEG molecules) (Sigma-Aldrich, US) prepared by lab scientists with appropriate authorisation and adhering to well described and tolerated approaches.9 Skin tests to polysorbate 80 (PS80, Sigma-Aldrich, US) were only conducted within this subset.

A further subgroup of patients underwent PEG 3350 IDT using depo-methylprednisolone (Pfizer Ltd, UK), a drug they were naïve to. Depo-medroxyprogesterone (Pfizer Ltd, UK) was used for IDT when it was the index drug in this sub-group. Depo-medroxyprogesterone IDT concentrations ranged from 0.203mg/mL (0.0203%) to 2.03mg/mL (0.203%) of PEG. Depo-methylprednisolone IDT concentrations ranged from 0.29mg/mL (0.029%) to 2.9mg/mL (0.29%) of PEG

In addition to skin testing using the index drug, reliant on test centre and availability, patients underwent skin testing to the PEG-free version of their index drug using non-irritant concentrations as recommended by the European Network on Drug Allergy (ENDA).10

*DPT*

Graded DPTs were performed to the index PEG-containing drug and either the PEG-free version of the index drug or macrogol (Galen Ltd, UK). Although protocols varied according to centre and patient risk, for all graded DPTs, the target cumulative dose equated to the typical recommended therapeutic drug dose.

*Statistical analysis*

Categorical variables were expressed as numbers and percentages and continuous variables as medians and ranges. Fisher’s exact testing was used to analyse non-parametric categorical data. A p value of <0.05 was considered statistically significant. Graphpad Prism (Graphpad Software Inc, California, US) was used for analyses.

Results:

*Demographics*

A total of 44 patients were investigated for suspected immediate PEG hypersensitivity. Ages ranged from 18 to 72 years, with a median age of 38 years and a mean age of 38.25 years. The female-to-male ratio was 2.7:1 (32 females: 12 males). Of the 30 with known medical co-morbidities, 16 were atopic with asthma, allergic rhinitis, eczema or food allergy (Table 1).

Time from first reaction to review in an allergy service ranged from 0.75 to 72 months, with a median time of 6 months. The number of immediate HSRs experienced prior to review ranged from 1 to 4.

*Index reaction*

In total, 70 different PEG-related drug reactions were associated with 44 patients. Two patients reported reactions to four, four patients to three, 12 patients to two and 26 patients reported reactions to one PEG-containing medication (Table 2). Of the 70 index drugs, 57% (40 of 70) were administered orally and 31% (22 of 70) administered intramuscularly (IM) or intravenously (IV) (Table 1).

Macrogol laxatives cumulatively were the most common index drugs reported (23%, 16 of 70), followed by depo-medroxyprogesterone (Pfizer Ltd, UK) (19%, 13 of 70), oral Penicillin V (Sandoz, UK) (10%, 7 of 70), and depo-methylprednisolone (Pfizer Ltd, UK) (10%, 7 of 70). Amongst the macrogol laxatives, Moviprep (Norgine Ltd, UK) (100,000 mg of PEG 3350 per sachet, n=7) and Movicol (Norgine Ltd, UK) (13,125 mg of PEG 3350 per sachet, n=6) were the most implicated. This was followed by Klean-prep (Norgine Ltd, UK) (59,000 mg of PEG 3350 per sachet, n=1), Laxido (Galen Ltd, UK) (13,125 mg of PEG 3350 per sachet, n=1) and Peglax (Casen Recordati, Spain) (10,000 mg of PEG 4000 per sachet, n=1) (Fig 1).

Among the 42 PEG-allergic patients, grade severity was detailed for 60 reactions. 57.1% (24 of 42) of patients investigated had experienced Brown’s Grade III anaphylaxis, 40.5% (17 of 42) had Grade II and only 2.4% (1 of 42) had Grade I reactions as their most severe reaction (Table E2)8. There was no significant difference in reaction grade between different routes of administration (Table 1).

In 19 reactions (involving 19 patients), acute and baseline serum mast cell tryptase (MCT) levels were measured. All 19 demonstrated a significant acute MCT rise with a median increase of 53 ug/L (range 13 – 114 ug/L). This equated to a median 9.1-fold increase (range 2.1 – 26.5-fold increase). Average (median) baseline and acute MCTs were 6.1 (range 3 -10) and 53 (range 13 - 114) respectively (normal range: 2.0-11.4 ug/L).

*Investigation results*

PEG hypersensitivity was confirmed in 95% (42 of 44) of cases investigated following positive SPT (n=24), IDT (n=15) or DPT (n=3).

*SPT and IDT results*

All 44 patients underwent PEG SPT (42 to PEG3350 and one patient to only PEG8000), concentrations ranged from 1mg/L (0.1%) to 100mg/mL (10%) of PEG. Of these, 26 patients were SPT-positive. However two SPT-positive patients, positive only to a MW PEG higher than their index PEG weight, underwent confirmatory IDT with the index MW before concluded to be PEG-allergic.

Among those confirmed PEG-allergic, 41 of 42 underwent SPT with PEG 3350 (10%). Sensitivity of SPT with PEG 3350 overall was 51% (21 of 41). PEG 3350 SPT sensitivity increased when macrogol laxatives or depo-methylprednisolone were implicated as index drugs to 71.4% (10 of 14) and 66.7% (4 of 6) respectively ( Table E4). IDT with PEG 3350 (PEG testing concentrations ranging from 0.0203% to 1%) was positive in 82% (14 of 17) of all patients tested. This increased overall skin test (SPT & IDT) sensitivity to 85% (35 of 41 patients tested with PEG3350).

Skin testing with higher molecular weight PEG was limited to a small group of nine patients with negative SPT and IDT to PEG 3350. In 8 of 9 patients SPT was positive with PEG 8000 and/or PEG 20.000 (0.1 - 10%). In one SPT (PEG3350 & 20,000) negative patient, IDT was positive with PEG 20,000 0.1%

PEG-free formulations of index drugs where available were tested in 18 patients. SPT and IDT test to these drugs were negative in all patients.

Five patients underwent PS80 SPT with only one patient demonstrating a positive result (PS80, Sigma-Aldrich US, 10%). This patient was IDT positive to a 100-fold dilution of triamcinolone acetonide (Kenalog, Bristol-Myers Squibb Ltd UK) containing 0.004 mg/mL of PS80 and IDT-negative to the preservative/excipient-free triamcinolone acetonide.

*DPT results*

Seven patients in total underwent DPT, five of which were DPT-positive. In two of the five patients, possible PEG allergy was only considered following positive DPT to their index drug (depo-methylprednisolone, Pfizer, UK). Both were PEG SPT-positive.

The remaining three patients were 10% PEG 3350 SPT-negative prior to DPT (Fig 2). One of three patients proceeded to a positive macrogol DPT without any prior IDT. The remaining two of three patients were IDT-negative to their index drug (0.029 % of PEG3350 in depo-methylprednisolone n=1, 0.203% of PEG3350 in depo-medroxyprogesterone n=1, and 0.0203% of PEG3350 in depo-medroxyprogesterone n=1).

Of note, one patient reacted on DPT to their index drug (depo-medroxyprogesterone, 20.3 mg of PEG 3350 per 1 mL) but tolerated a subsequent macrogol oral DPT (cumulative1 macrogol powder sachet containing13,125 mg of PEG3350).

PEG tolerance was confirmed in 4.5% (2 of 44) patients following negative macgrogol or depo-methylprednisolone DPTs with preceding negative SPT and IDT to PEG3350 and/or index drug. While both were concluded to be PEG-tolerant, it was noted one patient only received the equivalent of ¼ of a sachet on macrogol DPT, reason not documented.

Among the five DPT-positive patients, symptoms included hypotension, tachycardia, urticaria, flushing, nausea, sneezing and cough or wheeze. Further details regarding DPT-positive patients are summarised in Table 3.

*Systemic reactions on skin testing*

Of the 44 patients investigated, one patient (2%) experienced a systemic reaction (urticaria and angioedema) to simultaneous 10% SPT to PEGs of various MWs ranging from 200 to 20,000. The patient was treated with intravenous hydrocortisone and oral H1 antihistamine.

Five patients experienced systemic reactions on IDT. IDTs were performed with 0.1 – 1 % macrogol laxatives and/or 0.203 – 0.0203% depo-medroxyprogesterone. Symptoms included chest tightness (n=3), generalised itch (n=2), urticaria (n=1), erythema (n=1) and rhinitis (n=1). Treatment included intramuscular adrenaline (n=1), corticosteroids (n=2), H1 antihistamines (n=4), and nebulised salbutamol and ipratropium bromide n=1). Two patients were previously SPT-positive to a higher MW PEG (SPT-negative to the index MW PEG and drug), the other three were SPT-negative to both the index PEG and drug. Two of five underwent simultaneous PEG IDT to more than one MW and/or concentration.

*PEG tolerance*

Of the 42 PEG-allergic patients, nine patients tolerated five different drugs where all brands were known to contain PEG. We collated data on PEG quantities sourced from the relevant pharmaceutical companies (Table 4). Seven of nine patients reported tolerating H1 antihistamines containing PEG (Table 4).

*COVID-19 vaccination*

Vaccination status could be determined in 21 patients. Of these, 16 were COVID-19 vaccinated. The number of COVID-19 vaccines administered ranged from 2-4 (median 3). At the point of review the majority had received three doses (n=7) or two doses (n=4) of the Oxford/AstraZeneca (AZ) COVID-19 vaccine. Three patients received and tolerated two AZ doses followed by a booster with either a Pfizer/BioNTech (0.05mg of PEG2000 per 0.3mL dose) or Moderna (PEG2000, quantity not disclosed) COVID-19 vaccine. One patient tolerated four doses of the Pfizer/BioNTech COVID-19 vaccine and a second patient tolerated two doses of the Pfizer/BioNTech COVID-19 vaccine.

Of the five patients who tolerated at last one dose of Pfizer/BioNTech or Moderna COVID-19 vaccine, four had previously experienced grade II and one patient grade III as their most severe index PEG drug reaction prior to COVID19 vaccination. In four patients the index PEG MW was 3350 and in a 5th patient the index PEG MWs ranged from 3350 to 20000.

Discussion:

We report the largest multi-centre cohort of patients investigated for PEG allergy. Our data highlights the existing knowledge and persisting uncertainties regarding investigating and diagnosing PEG hypersensitivity. A high index of suspicion, familiarity with complex and often confusing PEG nomenclatures and greater awareness of the drugs often associated with PEG hypersensitivity are required to facilitate correct and timely diagnosis.11

Of the 23 different drugs implicated in index reactions, grouping laxatives and bowel preparations together, 16 contained PEG MWs ≥ 3350 (Fig 1). Our data suggests PEG hypersensitivity generally occurs with drugs containing the excipient at a MW of 3350 and above. This is supported by the fact that a number of patients tolerated the Pfizer/BioNTech COVID-19 vaccine (containing 0.05mg PEG2000) and the low rates of adverse reactions to the vaccine reported worldwide.12

We have collected valuable data regarding the per unit mg PEG quantities of commonly implicated drugs (Table 4, Table E3 and Table E5) obtained following requests to the relevant pharmaceutical companies. Among our cohort, the commonly implicated drugs contained larger quantities of PEG. Macrogol laxative preparations contained the highest PEG quantities (10,000 – 100,000 mg of PEG3350 per sachet). This was followed by depo-methylprednisolone (29 mg of PEG3350 per 1mL), depo-medroxyprogesterone (20.3 mg of PEG3350 per 1mL) and penicillin V (6mg of PEG6000 per 250mg tablet) (Table E5).

Among the macrogol laxatives, preparations with higher PEG content were not more frequently implicated, suggesting above a certain threshold dose there may not be an increase in reaction risk.

While the average age of our cohort is compatible with literature describing a younger median age of diagnosis, our female predominance diverged from the previously reported male predominance.13,14 PEG allergy presented as a severe immediate hypersensitivity reaction with 61% of our cohort experiencing grade III anaphylaxis with a concomitant significant rise in mast cell tryptase, where measured. This is also supported by previous smaller case series.4, 6, 15 43% of this cohort also reported reacting to two or more PEG-containing medications.

Standardised reagents for skin testing to PEG are not yet commercially available. An international consensus on skin testing concentrations and use of PEG of different MWs is needed. Among our cohort the SPT concentration of PEG in the culprit drugs (available as intravenous preparations) ranged from 0.491% (4.91 mg/mL) to 2.9% (29 mg/mL). Macrogol laxatives had the highest PEG concentrations for SPT at 10% (100mg/mL). The difference in PEG concentrations may explain 4 patients being macrogol SPT-positive and index drug SPT-negative. We would therefore suggest to always conducting SPT with PEG 3350 10%.15

Our data confirms, in our selected cohort with a high pre-test probability, IDT does increase diagnostic sensitivity relative to SPT alone. The risk of systemic reactions on IDT appears to increase if multiple IDTs are conducted (median of 3 IDTs conducted simultaneously, range 2-5). However, only a small number of our total cohort (n=5) experienced IDT-associated systemic reactions, all of which were managed promptly. IDT is at present still a key part of PEG investigations but must be used appropriately and with precautions, prior consent and conducted by experienced clinicians in an appropriate setting.

Garvey et al described the potential role of higher MW PEG SPT as a means of increasing SPT sensitivity. 6, 9 This was confirmed in two of our patients who were SPT-positive to higher MW PEGs and PEG DPT positive. An additional two patients who were SPT-positive to a higher MW PEG were subsequently IDT-positive to their index MW PEG.

However SPT with higher MW PEGs also carries a risk of systemic reactions (11%, 1 of 9 PEG-allergic who underwent HMW PEG SPT testing).6, 9 The validity of this approach requires confirmation in a larger number of patients. Currently higher MW PEG preparations are not routinely available, making this potentially useful approach difficult to implement in clinical practice.16

In skin test negative patients who require DPT, it is important to consider the following points. PEG is likely more allergenic with higher MWs and doses capable of crossing patient thresholds.6 Gastrointestinal absorption of higher MW PEGs >1000 g/mol can be as low as 2%.17 A case of previous anaphylaxis to depo-methylprednisolone (29 mg/mL of PEG 3350), requiring cumulative 7100mg of oral macrogol to elicit a reaction on PEG DPT, suggests gastrointestinal absorption in some cases may be even less than 2%.18 In such patients, greater oral PEG quantities may be required during DPT, to reach their threshold. Until PEG gastrointestinal absorption behaviours are more precisely understood, negative oral DPT with a single sachet macrogol (therapeutic dose), can be of questionable diagnostic value. Studies are required to better understand PEG thresholds and PEG equivalent doses of various route of administration. Among our cohort there was one possible false negative macrogol DPT, given the convincing clinical history, positive DPT to the index drug and negative DPT to the active ingredient (PEG-free version).

Only six patients in our cohort underwent skin testing to explore PS80 cross-reactivity. With one confirmed case of hypersensitivity to both PEG and PS80. Cases of PS80 cross-reactivity have been clinically reported in small numbers. The true risk of cross-reactivity between PEG and PS80 due to its shared chemical moiety: : –(CH2CH2O)*n* warrants further investigations.4, 14

Our data has allowed us to explore the tolerance of some PEG-containing drugs in PEG-allergic patients (Table 4, Table E5). Nine PEG-allergic patients tolerated PEG-containing drugs. Seven of nine tolerated H1 antihistamines. The reason for this is unknown but possibly related to their H1 receptor antagonistic properties. There appears to be no pattern suggesting tolerance of PEG in lower doses or MWs when compared to the index drug (Table 4). Others, like us, have reported tolerance of Pfizer/BioNTech vaccine (PEG2000: 0.05mg) in PEG-allergic patients who had reacted to PEG-asparaginase and bowel preparation, which may be due to threshold doses and lower MW. 15,19

Among our PEG-allergic group, tolerance of six other possible PEG-containing drugs was described. Unfortunately the presence or absence of PEG varied according to drug brand (Table E5) and brand details were not documented in clinical records. As a result no further conclusions regarding PEG tolerance could be made. This highlights the importance of sourcing manufacturer/brand details when obtaining a drug history in patients with suspected PEG allergy.

Low rates of immediate hypersensitivity reactions to the Pfizer/BioNTech COVID-19 vaccine (0.05mg PEG2000) due to PEG allergy are described. Currently Centers for Disease Control and Prevention (CDC) and the UK Health Security Agency’s Green Book guidance recommend the use of an alternative COVID-19 vaccine following anaphylaxis to a COVID-19 vaccine dose or prior allergic reactions to a COVID-19 vaccine excipient. 20,21

However, five PEG-allergic patients in our cohort tolerated at least one PEG-containing mRNA vaccine with one patient tolerating four doses of the Pfizer/BioNTech COVID-19 vaccine. Similarly, a recent clinical observation found only five of the 65 patients reporting immediate reactions on first-dose mRNA vaccination had evidence of PEG sensitisation on skin testing. All who agreed to second dose mRNA administration (n=3) tolerated vaccination despite their sensitisation and history on first mRNA dosing.22

In keeping with previous work demonstrating tolerance of PS80 containing COVID-19 vaccines in PEG allergic patients, 14 patients in our cohort tolerated at least one AZ dose.23

The relationship between PEG tolerance and drug pharmacological properties, mode of delivery and PEG MW and doses requires further evaluation with larger data to be fully understood.16 At present patients are advised to avoid all PEG-containing drugs., Once further information is available allergists may be able to offer more practical advice after diagnosing PEG allergy.

In conclusion, PEG allergy affects more women than men at a younger age than that commonly seen in other drug hypersensitivities. Reactions are mostly severe and occur with different drug classes and routes of administration. The commonly implicated drugs are macrogol laxatives, depo-medroxyprogesterone (Pfizer Ltd, UK), oral Penicillin V (Sandoz, UK), and depo-methylprednisolone (Pfizer Ltd, UK).The potential role of SPT with alternative MW PEGs requires further attention. PEG IDTs should be conducted with precautions to mitigate the associated risks of systemic reactions. While the retrospective data collection, variations in investigative practices and documentation are study limitations, our study offers valuable first-time data regarding the per unit mg PEG quantities. This has highlighted the need for further studies to better understand PEG thresholds and PEG equivalent doses of various route of administration, as well as the implications of specific drug pharmacokinetics.

**Figure 1: Index drugs reported**

**Table 1: Demographics and Index reaction**

**Figure 2: Investigation results**

**Table 2: Index drugs reported for each patient**

**Table 3: DPT-positive patient details**

**Table 4: Comparison of PEG MW and quantities between index drugs and PEG drugs tolerated**

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