

Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized



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What is already known about this topic? The most common immediate hypersensitivity to macrogols is associated with polyethylene glycol (PEG) 3350; however, the epidemiology, mechanisms, and cross-reactivity are poorly understood. Thousands of medications contain either PEGs or structurally similar polysorbates.

What does this study add to our knowledge? *In vivo* and *ex vivo* testing of 2 cases suggest an IgE-mediated type I hypersensitivity mechanism to PEG 3350 anaphylaxis. This hypersensitivity, while rare, may be more common than we recognize.

How does this study impact current management guidelines? Immediate hypersensitivity to PEG 3350 with cross-reactive polysorbate 80 hypersensitivity may be underrecognized in clinical practice and can be evaluated with clinical skin testing.

BACKGROUND: The most common immediate hypersensitivity to macrogols is associated with polyethylene glycol (PEG) 3350; however, the epidemiology, mechanisms, and cross-reactivity are poorly understood. Thousands of medications contain either PEGs or structurally similar polysorbates. **OBJECTIVE:** Our objective was to better understand the mechanism, cross-reactivity, and scope of PEG hypersensitivity. **METHODS:** Two cases with a past history of immediate hypersensitivity to PEG-containing medications were used to study potential mechanisms and cross-reactivity of immediate reactions to PEG 3350. Skin testing and oral challenges with PEG and polysorbate-containing agents were employed to determine clinical reactivity and cross-reactivity between the 2 allergens. Enzyme-linked immunosorbent assay and electrochemiluminescent immunoassay were used to detect anti-PEG specific IgG and IgE, respectively, using PEGylated protein or PEG alone as antigens in 2 cases and 6 PEG 3350 tolerant controls. We searched US Food and Drug Administration (FDA) adverse

event reports for immediate reactions to PEG 3350 to determine the potential scope of this problem in the United States.

RESULTS: Skin and provocation testing demonstrated symptomatic reactivity in both cases to PEG 3350 and polysorbate 80. Plasma samples were positive for anti-PEG specific IgE and IgG antibodies only in cases and binding increased directly proportional to the molecular weight of PEG tested. FDA adverse event reports revealed 53 additional cases of possible PEG 3350 anaphylaxis.

CONCLUSIONS: Immediate hypersensitivity to PEG 3350 with cross-reactive polysorbate 80 hypersensitivity may be underrecognized in clinical practice and can be detected with clinical skin testing. Our studies raise the possibility of an IgE-mediated type I hypersensitivity mechanism in some cases. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1533-40)

Key words: Polyethylene glycol; PEG; Immediate hypersensitivity; Allergy; Polysorbate

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Abbreviations used

CI- Confidence interval
 ELISA- Enzyme-linked immunosorbent assay
 FDA- US Food and Drug Administration
 MW- Molecular weight(s)
 OD- Optical density
 PEG- Polyethylene glycol
 sIgG- Specific IgG

Macrogols, including polyethylene glycols (PEGs) and the structurally related polysorbates (Figure 1), are compounds whose primary feature includes polyether groups. They have wide ranging use in medical and commercial settings, with molecular weights (MW) that range from 200 to 35,000 g/mol.¹ PEGs of MW between 3350 and 6000 are frequently used as excipients in many liquid and solid formulations of medications.^{2,3} PEG of MW 5000 is used in conjugated enzyme therapeutics, such as PEG-asparaginase and PEG-adenosine deaminase, to improve drug pharmacokinetics and lower immunogenicity. PEG of MW 3350 is the primary ingredient in commonly used oral bowel preparations for colonoscopy procedures in the United States.^{1,4} Recently, PEGs of this MW range have received attention as a cause of anaphylaxis to preparations used for colonoscopies,⁵ and as an immunogenic epitope in PEGylated asparaginase (Oncaspar and Pegcrisantaspase).^{6,7} There is only limited awareness of their role in reactions to medications where they are present as an excipient.^{4,8-10} Many patients report repeated cutaneous exposures¹¹⁻¹⁴ or local reactions to PEG-containing topical items¹⁵ before the onset of systemic reactions to high-molecular-weight PEG-containing medications, suggesting a cutaneous mode of sensitization. Gastrointestinal sensitization has been theorized in PEG allergic patients with an impaired epithelial barrier.¹⁶⁻¹⁸ However, the scope to which macrogol hypersensitivity might be a problem in the United States and the mechanism for PEG and polysorbate reactions are not well understood.^{8,19,20} After encountering 2 cases of life-threatening immediate hypersensitivity to macrogols in our clinic, we sought to further understand the mechanism and scope of immediate hypersensitivity to PEG.

METHODS**Clinical surveillance**

Cases were recruited through a dedicated drug allergy clinic at Vanderbilt University Medical Center. A detailed clinical case description was obtained from patients whose history suggested an immediate reaction to PEG 3350-containing colonoscopy preparations, laxatives, or injected corticosteroids during a 3-year period. This study was done under institutional review board (IRB) approved protocols from Vanderbilt University (Vanderbilt IRB #61455).

Skin testing and challenges

To determine clinical reactivity to macrogols, including PEGs and polysorbate-containing products, we used a combination of skin prick, intradermal, and challenge testing with standard methodologies.²¹

Controls

Two healthy adult volunteers served as negative controls for the skin testing protocol. Six additional healthy adult volunteers with previous exposure to PEG 3350 during colonoscopy preparation or use of laxatives during the last 5 years provided blood samples used as controls during laboratory assays.

Laboratory methods

To better understand the mechanism of macrogol hypersensitivity in the 2 cases, we next sought to detect the presence of PEG specific antibodies. Enzyme-linked immunosorbent assay (ELISA) was used for the detection of anti-PEG antibodies. Briefly, Corning 96-well enzyme immunoassay/radioimmunoassay (EIA/RIA) assay microplates were coated with 5000 g/mol methoxy-PEG-*Escherichia coli* asparaginase (Oncaspar) at 10 µg/mL. For anti-PEG IgG detection, plasma samples obtained from the aforementioned 2 cases 2 to 3 months after their last anaphylaxis episodes were incubated at 1:400 dilution. For anti-IgE detection, the same plasma samples were pretreated with Protein G Plus Agarose (Thermo Fisher Scientific, Waltham, Mass) at a 1:1 ratio to remove IgG and then incubated at 1:10 dilution. Horseradish peroxidase (HRP)-conjugated goat anti-human IgG (Sigma-Aldrich, St. Louis, Mo) or anti-human IgE (BioRad, Hercules, Calif) antibodies were added at 1:1000 and 1:10,000 dilution, respectively. Plates were read at dual wavelengths of 490 nm and 630 nm on an ELx808 microplate reader (BioTek, Winooski, Vt). Plasma samples from 6 patients with similar exposure to colonoscopy preparations containing macrogols were used as controls.

To better determine the presence or absence of PEG specific IgE, we next used an electrochemiluminescent method with greater sensitivity for detection. Standard MULTI-ARRAY 96-well SECTOR plates were coated with Oncaspar and 5000 g/mol methoxy-PEG-bovine catalase at 10 µg/mL. The samples were processed with Protein G Plus Agarose as described above and then incubated at 1:10 dilution. A biotin-conjugated goat anti-human IgE (BioRad) antibody was added at 1:10,000 dilution. SULFO-TAG labeled Streptavidin was used as the detection reagent. Plates were read with a Sector Imager 6000 Analyzer (Meso Scale Discovery, Rockville, Md).

Furthermore, to investigate the effect of the molecular size of unconjugated PEG on anti-PEG specific IgG (sIgG) binding, we coated Nunc Maxisorp 96-well microplates (Thermo Fisher Scientific) with 5 µg/mL HO-PEG-NH₂ of MW ranging from 1 to 10 kDa (Creative PEGWorks, Durham, NC). Case and control samples were incubated at 1:100 dilution. Other steps were the same as the anti-Oncaspar IgG detection ELISA mentioned above.

Public data review

To evaluate the scope to which PEG 3350 might be associated with anaphylaxis in the United States, we next undertook a review of the publicly available FDA Adverse Event Reporting System database from 1989 through 2017. Using the search terms “polyethylene glycol” and “anaphylactic shock” or “anaphylactic reaction” we reviewed the number of these complaints for PEG-containing colonoscopy preparations and laxative products. We evaluated cases associated with branded and generic colonoscopy and laxative products whose primary ingredient was PEG 3350, including colonoscopy products both with and without electrolytes.

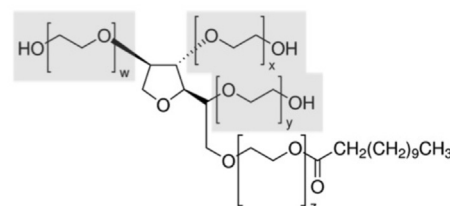
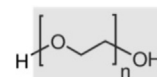
Medication excipient review

To evaluate the degree to which immediate hypersensitivity to PEG 3350 or polysorbate 80 might affect medication or vaccine safety for affected patients, we next reviewed publicly available data in the searchable “DailyMed” database provided by the National

RESULTS

During our 3-year period of surveillance, we encountered 2 patients with a history of anaphylaxis during preparation for colonoscopy and after methylprednisolone acetate injections.

The second patient was a 51-year-old man with an occupational history as a mechanic exposed to glycol-containing hydraulic fluids, presenting for evaluation due to concern for perioperative anaphylaxis. Four months before presentation, he was to receive an outpatient c-spine epidural steroid injection for cervical spine degeneration. He received lidocaine followed by



omnipaque and methylprednisolone acetate. Within 5 minutes after the procedure he became itchy, red, hypotensive and a code was called. He was given ondansetron and methylprednisolone sodium succinate in addition to IV fluids. He was taken to the emergency department where he noted swelling in his hand, itching, difficulty swallowing, and hoarseness. He was given epinephrine as well as IV diphenhydramine and famotidine. He was admitted to the ICU for observation. One month before presentation, he began to develop a reaction just before a scheduled colonoscopy after the use of a PEG 3350 colonoscopy preparation. He became hypotensive and flushed and was treated with diphenhydramine, epinephrine, and IV fluids.

The 3 bowel preparations and methylprednisolone acetate to which the patients had experienced immediate hypersensitivity reactions all share the ingredient PEG 3350. Both patients subsequently underwent prick and intradermal skin tests with serial dilutions of common corticosteroids, including methylprednisolone acetate (containing PEG 3350), methylprednisolone succinate (containing neither PEG nor polysorbate 80), betamethasone (containing neither PEG nor polysorbate 80), dexamethasone (containing neither PEG nor polysorbate 80), and triamcinolone acetonide (containing polysorbate 80, which shares significant structural homology to PEG) (Table I). During intradermal testing to the steroid preparations, patient 1 developed a sensation of throat and body itching, with a visible urticarial rash expanding from testing sites, which was alleviated with 10 mg of cetirizine and 300 mg of ranitidine, without necessitating further treatment with epinephrine (Figure 2). Patient 1 was subsequently demonstrated to have skin test positivity to other polysorbate 80-containing products, including eye drops and conjugated pneumococcal vaccine, but was able to asymptotically tolerate a low-molecular-weight PEG oral challenge with PEG 300. Although patient 2 had negative prick testing to PEG 3350-containing products and negative intradermal skin testing to methylprednisolone acetate, he did have positive testing to triamcinolone acetonide—containing polysorbate 80. On challenge with PEG 3350 he developed diffuse urticaria, respiratory distress, and hypotension requiring epinephrine and emergency department transfer. Both patients were able to tolerate challenge with parenteral steroids that did not contain macrogols.

TABLE 1. Skin prick and intradermal testing with corticosteroids and polyethylene glycols

Agent (concentration)	Patient 1			Patient 2		
	Wheal (mm)	Flare (mm)	Interpretation	Wheal (mm)	Flare (mm)	Interpretation
Skin Prick Test Results						
Histamine control (0.1 mg/mL)	6	26	Positive	7	20	Positive
Saline	0	0	Negative	0	0	Negative
PEG 3350	10	26	Positive	0	0	Negative
PEG 3350 (1:10 dilution)	11	22	Positive	0	0	Negative
PEG 3350 (1:100 dilution)	11	29	Positive	0	0	Negative
PEG 300 (1:10 dilution)	0	0	Negative			
PEG 300 (1:100 dilution)	4	5	Negative			
Methylprednisolone acetate	5	12	Positive	0	0	Negative
Methylprednisolone sodium succinate	3	3	Negative	0	0	Negative
Intradermal Skin Test Results						
Betamethasone (6 mg/mL)	6	6	Negative	0	0	Negative
Betamethasone (0.6 mg/mL)	5	5	Negative	0	0	Negative
Dexamethasone (0.4 mg/mL)	5	0	Negative	0	0	Negative
Dexamethasone (0.04 mg/mL)	7	0	Negative	0	0	Negative
Methylprednisolone sodium succinate (5 mg/mL)	5	6	Negative	0	0	Negative
Methylprednisolone sodium succinate (0.5 mg/mL)	0	0	Negative	0	0	Negative
Methylprednisolone acetate (4 mg/mL)				0	0	Subacute response developed at 20 h, with 14 mm raised wheal
Methylprednisolone acetate (0.4 mg/mL)				0	0	Negative
Triamcinolone acetonide (1 mg/mL)	10	19	Positive	10	30	Positive
Triamcinolone acetonide (0.1 mg/mL)	15	24	Positive			
Conjugated pneumococcal vaccine (w/polysorbate 80)	20	35	Positive			
Conjugated pneumococcal vaccine (1:10 dilution)	21	30	Positive			
Polysorbate 80-containing eye drop (1:10 dilution)	15	30	Positive			

Two healthy adult controls underwent PEG testing on the same day as patient 2, with negative testing and no irritation at testing sites.

Laboratory results

Anti-PEG specific antibody concentrations were measured as optical density (OD) from the ELISA using methoxy-PEG-*E. coli* asparaginase as the antigen source. Anti-PEG sIgG ODs in plasma samples from the 2 cases (0.50 for patient 1 and 0.31 for patient 2) were significantly higher than that of the 6 PEG-exposed controls (99% confidence interval [CI] = 0.025 ± 0.019), indicating that both cases were positive for anti-PEG sIgG in these samples obtained 2 to 3 months after the last reaction (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Anti-PEG sIgE readings for the patients were negative by this method: ODs were 0.045 and 0.020 respectively for patients 1 and 2 compared with controls of 0.019 ± 0.0037 , none of which were above the uncoated well-background signal (99% CI = 0.050 ± 0.011).

Using the more sensitive Meso Scale Discovery electrochemiluminescence method we were then able to detect sIgE directed against PEG in our 2 cases, but not our controls. Luminescence intensity from the 2 cases against Oncaspar (88 for patient 1 and 77 for patient 2) was significantly higher than that of the controls (99% CI = 55.9 ± 4.1). Similarly, luminescence intensity from the 2 cases against PEG-bovine catalase (246 for patient 1 and 194 for patient 2) was significantly higher than that of the controls (99% CI = 54.3 ± 9.3). The increase in luminescence intensity against both PEG-containing reagents, when tested with sufficient sensitivity, indicates that both cases were positive for anti-PEG sIgE (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Using unconjugated PEG molecules of different sizes as the antigen source, samples from both cases showed strong preference toward PEGs of larger molecular weights (Figure 3). Although patients in both cases reacted clinically to PEG 3350, anti-PEG sIgG antibodies in their plasma samples displayed even higher binding for higher molecular weight PEG 5k and PEG

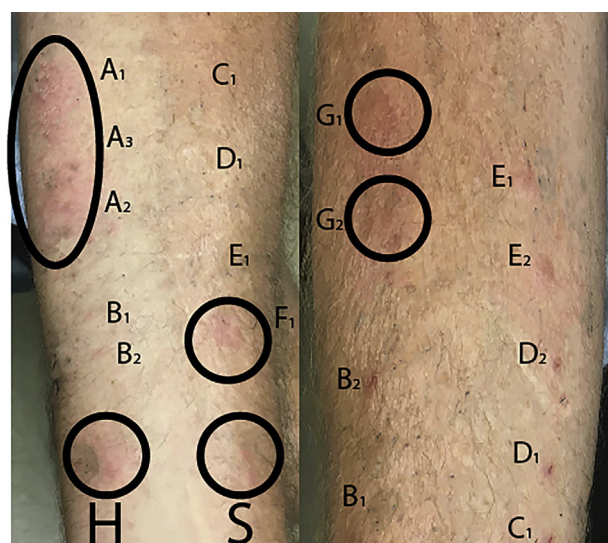


FIGURE 2. Selected skin testing images for patient 1: in the left panel is skin prick testing read at 15 minutes demonstrating positive responses to methylprednisolone acetate (MP acetate), and polyethylene glycol 3350 (PEG 3350). Other tested corticosteroids were negative. In the right panel is intradermal testing read at 15 minutes, which demonstrates a positive response to triamcinolone acetate at 1 and 0.1 mg. Other tested corticosteroids were interpreted as negative (Measurements are recorded in Table I). Key: drug used is indicated by the letter. A = polyethylene glycol 3350 (Miralax), B = methylprednisolone sodium succinate 5 mg/mL, C = budesonide 0.6 mg/mL, D = dexamethason 0.4 mg/mL, E = hydrocortisone 5 mg/mL, F = methylprednisolone acetate 4 mg/mL, G = triamcinolone acetate 1 mg/mL. A subscript 1 = full strength, a subscript 2 = 1:10 dilution, and a subscript 3 = 1:100 dilution.

10k, and almost no binding toward the lowest molecular weight PEG 1k (ODs were 0.021 and 0.014, respectively) compared with controls (99% CI = 0.014 ± 0.006) who did not demonstrate binding at any molecular weight of PEG.

Public data review results

Using the preferred search term “anaphylactic” to capture both “anaphylactic shock” and “anaphylactic reaction,” we encountered 25,905 reports to the FDA between 1989 and the end of 2017. When the additional term “polyethylene glycol” was applied, we were left with 133 reports associating PEG with anaphylaxis. Of these, we encountered 53 reports with unique case identifiers described as either anaphylactic shock or an anaphylactic reaction in which PEG-containing bowel preparations or laxatives were the primary or sole agent suspected as causal (Table II). The average age at reaction was 48.9 years (23% missing data), and 51% of those who reacted were male (15% missing data). At the time of reaction, 51% reported that the PEG-containing product was the sole agent they had ingested before anaphylaxis and were not using any other concomitant therapies. The other 49% were taking other concomitant therapies at the time of reaction, but their reports indicated that primary suspicion was on PEG-containing products. In terms of the clinical context, 72% of the reactions occurred before

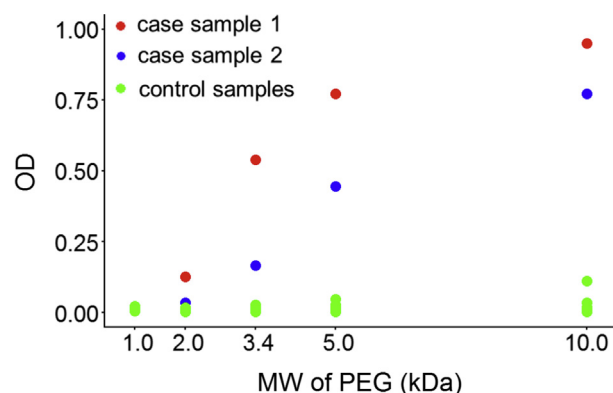


FIGURE 3. IgG optical densities (ODs) of case and control plasma samples against HO-PEG-NH₂ of different molecular sizes. MW, Molecular weight; PEG, polyethylene glycol.

colonoscopy preparation, and 28% occurred during the treatment of constipation. Reported reactions were distributed across the time period from 2005 to 2017, with an average of 4 cases reported per year during this time period (Figure 4). We did not encounter any reports of PEG-related reactions before 2005.

Medication excipient review

Using the search term “polyethylene glycol 3350” as an active or inactive ingredient returned 1155 FDA approved medications. A summary of the first 1000 hits can be found in Table E2 (available in this article’s Online Repository at www.jaci-inpractice.org). This list demonstrates that PEG 3350 can more commonly be found in film-coated tablets, topical gels, and parenteral steroids. Using the search term “polysorbate 80” as an active or inactive ingredient returned 6821 FDA approved medications. A summary of the first 1000 hits can be found in Table E3 (available in this article’s Online Repository at www.jaci-inpractice.org). This list demonstrates that polysorbate 80 can more commonly be found in film-coated tablets, parenteral steroids, and vaccines.

DISCUSSION

The most commonly known clinical use of macrogols such as PEG 3350 is in colonoscopy preparation or constipation treatment.^{5,23,25,26} However, a review of common products and the literature demonstrates that PEG and structurally similar polysorbate compounds can be found in vascular graft materials,¹⁰ surgical gels,²⁷ PEGylated medications,^{28–30} household and industrial compounds,¹ and as an excipient in a multitude of other medications both injectable and oral.^{4,31} In these settings, PEGs and polysorbates are not consistently described in ingredient lists.⁸ The National Institutes of Health DailyMed online resource through the National Library of Medicine is a useful resource for determining an individual product’s excipient content of macrogols such as PEGs and polysorbates.⁴ Although cutaneous and systemic reactions to film-coated tablets have been reported in patients with PEG hypersensitivity,⁸ both of our patients were otherwise healthy and taking no daily medications that contained PEG. Neither one is known to have reacted to any products other than what we have described in this report.

TABLE II. Cases of anaphylaxis reported to the FDA from 2005 to 2017 where polyethylene glycol 3350—containing formulations of colonoscopy preparation or laxatives were the primary drug suspected

FAERS report ID number	Age	Sex	Year of report	Formulation of PEG	Patient taking any other medications concomitantly	Indication (colonoscopy preparation vs constipation)
4852819-0	N/A	N/A	2005	Golytely	No	Preparation
4885400-8	30	Male	2005	Colyte	No	Preparation
5347102-3	42	Male	2007	Moviprep	No	Preparation
5326935-3	33	Female	2007	Polyethylene glycol 3350, brand not specified	No	Constipation
5792732-8	68	Male	2008	Golytely	No	Preparation
5829663-0	N/A	N/A	2008	Moviprep	No	Preparation
5909593-6	N/A	N/A	2008	Miralax	Yes	Constipation
5923262-8	64	Male	2008	Miralax	Yes	Constipation
6187140-4	52	Male	2009	Moviprep	Yes	Preparation
6262262-8	N/A	N/A	2009	Miralax	Yes	Preparation
6301790-3	52	Male	2009	Moviprep	Yes	Preparation
6446535-1	30	Female	2009	Moviprep	Yes	Preparation
6567457-1	N/A	N/A	2010	Polyethylene glycol 3350, brand not specified	Yes	Preparation
6583005-4	N/A	N/A	2010	Moviprep	No	Preparation
6625930-1	N/A	N/A	2010	Moviprep	No	Preparation
6649325-X	55	Female	2010	Golytely	Yes	Preparation
6681659-5	4	Male	2010	Miralax	No	Constipation
6784081-6	73	Male	2010	Miralax	No	Constipation
7610318-7	19	Male	2011	Moviprep	Yes	Preparation
7429359-8	59	Female	2011	Polyethylene glycol 3350, brand not specified	Yes	Preparation
7444601-5	55	Male	2011	Miralax	No	Preparation
7636123-3	64	Female	2011	Moviprep	No	Preparation
7759201-7	33	Female	2011	Polyethylene glycol 3350, brand not specified	No	Preparation
8274426-2	67	Female	2012	Moviprep	Yes	Preparation
8289679-4	57	Female	2012	Polyethylene glycol 3350, brand not specified	Yes	Constipation
8456637-6	46	Female	2012	Polyethylene glycol 3350, brand not specified	Yes	Constipation
8712178	N/A	Female	2012	Miralax	No	Constipation
8814458	24	Male	2012	Polyethylene glycol 3350, brand not specified	Yes	Constipation
9321913	16	Female	2013	Miralax	No	Preparation
9417033	56	Female	2013	Golytely	Yes	Preparation
9420162	N/A	Female	2013	Miralax	Yes	Constipation
9607762	50	Male	2013	Golytely	No	Preparation
9782506	70	Female	2013	Moviprep	No	Preparation
9828607	34	Female	2014	Miralax	Yes	Preparation
9894648	N/A	Female	2014	Miralax	Yes	Constipation
9934430	54	Male	2014	Miralax	Yes	Constipation
10235381	87	Female	2014	Moviprep	Yes	Preparation
10242352	13	Male	2014	Miralax	No	Constipation
10335513	54	Female	2014	Glycolax	No	Preparation
10428179	65	Male	2014	Moviprep	Yes	Preparation
10682474	59	Male	2014	Moviprep	No	Preparation
10710219	19	Female	2015	Moviprep	Yes	Preparation
11362693	N/A	N/A	2015	Miralax	No	Preparation
11573598	N/A	Female	2015	Moviprep	No	Preparation
11617696	74	Male	2015	Moviprep	No	Preparation

(continued)

TABLE II. (Continued)

FAERS report ID number	Age	Sex	Year of report	Formulation of PEG	Patient taking any other medications concomitantly	Indication (colonoscopy preparation vs constipation)
12787790	62	Male	2016	Polyethylene glycol 3350, brand not specified	Yes	Preparation
12849324	39	Male	2016	Colyte	Yes	Preparation
12865113	59	Male	2016	Polyethylene glycol 3350, brand not specified	No	Preparation
13243846	46	Male	2016	Moviprep	Yes	Preparation
13268930	64	Male	2016	Polyethylene glycol 3350, brand not specified	No	Preparation
13747359	68	Female	2017	Miralax	Yes	Constipation
13854981	73	Female	2017	Golytely	No	Preparation
13870252	61	Female	2017	Moviprep	No	Preparation
13896629	2	Male	2017	Golytely	Yes	Constipation

Data marked as N/A indicate that the information was not contained in the primary report to the FDA.

FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; PEG, polyethylene glycol.

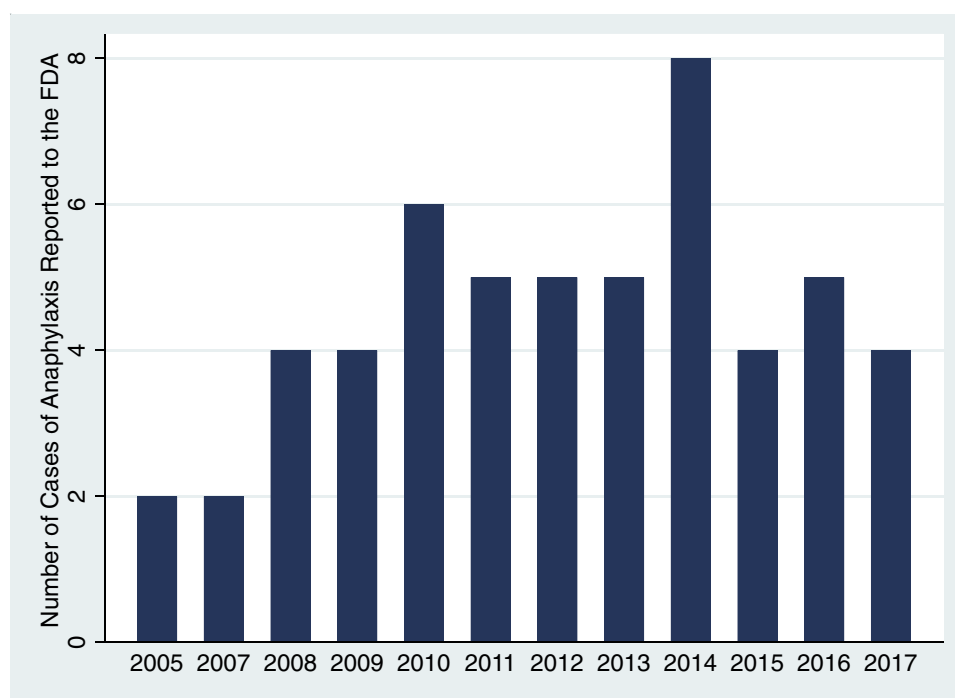


FIGURE 4. Cases of anaphylaxis reported to the FDA (FAERS) implicating PEG containing bowel preparations or laxatives, by year. FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; PEG, polyethylene glycol.

A recent review of published case reports and case series in the literature by Garvey et al found 37 cases of PEG hypersensitivity since 1977.⁸ Our review of the FDA data adds a large number of additional cases that may not have been noticed in the medical literature. Our data suggest that an average of 4 cases per year of PEG-associated anaphylaxis during colonoscopy preparation or laxative use are reported to the FDA. However, it is clear that relying on patient- or physician-initiated reports to the FDA will understate the true volume of the problem. Our review of FDA adverse event data focused only on drugs that contained pure PEG 3350 at concentrations of grams per dose. Therefore, we cannot

currently offer much additional data on whether drugs containing PEG or polysorbate 80 as an excipient at milligram or microgram concentrations can precipitate reactions in sensitized patients. We can only report that both of our patients have had anaphylaxis on parenteral exposure to methylprednisolone acetate, formulations of which typically contain around 29 mg/mL of PEG 3350.⁴

The mechanism for macrogol hypersensitivity has been poorly understood. Anti-PEG sIgG has been detected in patients receiving PEG-conjugated protein therapeutics,⁶ but was not studied in unconjugated macrogol anaphylactic cases, whereas anti-PEG sIgE has not been directly measured in any human

studies.³² Our findings of skin test reactivity and coexisting PEG-directed sIgE and sIgG antibodies suggest that an IgE-mediated type I hypersensitivity could be possible in clinical reactions to unconjugated macrogols. These cases may represent a separate phenotype of immediate hypersensitivity from what has been previously shown during reactions to PEG asparaginase and other PEGylated compounds.^{7,33} Of note, the absence of binding between patient IgG antibodies and lower MW PEGs also coincided with the tolerance of PEG 300 in both skin and oral challenges *in vivo*, supporting the involvement of antibodies specific for higher MW PEGs in the clinical reactions. The stronger reactivity of the patient samples against PEGs of higher molecular weight suggests that sensitization and risk of future reactions may depend partially on the molecular weight of PEG antigen exposures, and suggest that PEG may act as the primary antigen even when not conjugated to drug molecules. Detection of sIgE directed against PEG required the use of the more sensitive Meso Scale Discovery electrochemiluminescence method and polysorbate-free testing reagents. Our results suggest that the development of blood testing as a modality in diagnosis of macrogol hypersensitivity may be possible.

CONCLUSIONS

High-molecular-weight PEGs are common excipients in a wide variety of medications, household products, and industrial products that may provide a vehicle for sensitization in a subset of susceptible individuals. Allergists should be aware that cross-reactive immediate hypersensitivity to polyether-containing compounds such as macrogols/PEGs and polysorbates can occur, that they may occur via a type I hypersensitivity mechanism, and that they may be underrecognized.

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TABLE E1. Specific IgE (a) and specific IgG (b) directed against PEG-conjugated substances in cases and controls, measured by luminescence intensity (a) and optical density (b)

Sample	PEG-asparaginase (Oncaspar)	PEG-catalase
(a) Specific IgE, measured by luminescence intensity*		
Case 1	88	245.75
Case 2	76.75	193.5
Control 1	59.5	57.25
Control 2	49	54.25
Control 3	58.75	49.75
Control 4	53.75	45.75
Control 5	57.5	70.25
Control 6	56.75	48.75
(b) Specific IgG, measured by optical intensity†		
Case 1	0.4985	0.6895
Case 2	0.309	0.4095
Control 1	0.0185	0.029
Control 2	0.0215	0.0865
Control 3	0.0095	0.0155
Control 4	0.061	0.108
Control 5	0.0245	0.0485
Control 6	0.0145	0.029

*Samples were read in duplicates, the whole assay was performed twice, and reported results are averages.

†Samples were read in duplicates, the whole assay was performed once, and results are averages.

TABLE E2. FDA and OTC polyethylene glycol 3350-containing products

Effective amount (strength)	Route of entry	Product group Drug indication category Condition treated	Product examples
Grams	Oral	Powder for solution	
		Bowel evacuant/laxative	Clearlax, Colyte, EZ2GO, Gavilax, GaviLyte, Glycolax, Golytely, Healthylax, Moviprep, Nulytely, polyethylene glycol 3350, TriLyte
Milligrams	Parenteral	Intramuscular	
		Contraceptive	Depo-Provera
		Steroid	Depo-Medrol, methylprednisolone acetate
		Intra-articular	
		Steroid	Depo-Medrol, methylprednisolone acetate
Micrograms/unknown	Oral	Film-coated tablet	
		<i>Cardiovascular</i>	
		Angina	Ranexa
		Essential hypertension	Amlodipine-atorvastatin, amlodipine-olmesartan, amlodipine-valsartan, amlodipine-valsartan-hydrochlorothiazide, Avalide, Azor, Byvalson, irbesartan-hydrochlorothiazide, labetalol, losartan, losartan-hydrochlorothiazide, moexipril-hydrochlorothiazide, valsartan, valsartan-hydrochlorothiazide
		Pulmonary hypertension	Letairis, sildenafil
		<i>Endocrine</i>	
		Diabetes	Glipizide-metformin, Invokamet, Invokana, Janumet XR, metformin, pioglitazone-metformin, Steglatro
		Fibrate	Gemfibrozil
		Statin	Amlodipine-atorvastatin, fluvastatin, rosuvastatin, simvastatin
		<i>Gastroenterology</i>	
		Gallstone dissolution	Ursodiol
		Primary biliary cirrhosis agent	Ocaliva
		<i>Infectious diseases</i>	
		Antibiotic	Amoxicillin, doxycycline, minocycline, Solodyn
		Antifungal	Griseofulvin, Noxafil, voriconazole
		Hepatitis C	Epclusa, Harvoni, Mavyret, Moderiba, Ribasphere Ribapak, Ribavirin, Technivie, Viekira
		HIV	Atripla, Descovy, Entecavir, Isentress, Kaletra, Norvir, Prezista, Stribild, Tybost, Zidovudine
		Malaria	Chloroquine, hydroxychloroquine
		<i>Neurology</i>	
		Dementia	Donepezil
		Migraine	Sumatriptan
		Pain	Aleve, Morphine ER, Tramadol, Xartemis XR
		Seizure	Briviact, Gralise, Keppra, Keppra XR, levetiracetam
		<i>Oncology</i>	
		Antineoplastic	Bosulif, Cotellic, Tagrisso, Zelboraf
		Aromatase inhibitor	Letrozole
		<i>Psychiatry</i>	
		Antipsychotic	Nuplazid
		Depression	Bupropion, desvenlafaxine, fluoxetine, protriptyline
		Insomnia	Eszopiclone
		<i>Rheumatology</i>	
		Rheumatoid arthritis	Xeljanz
		<i>Urology</i>	
		Erectile dysfunction	Sildenafil
		Overactive bladder	Trospium
		<i>Other</i>	
		Anticoagulation	Xarelto

(continued)

TABLE E2. (Continued)

Effective amount (strength)	Route of entry	Product group Drug indication category Condition treated	Product examples
		Antihistamine	Cetirizine, hydroxyzine
		Chelating agent	Ferriprox
		Cystic fibrosis	Kalydeco, Orkambi
		Phosphate binder	Sevelamer
	Tablet		
		<i>Cardiovascular</i>	
		Angina	Metoprolol tartrate, nitroglycerin
		Antiplatelet	Clopidogrel
		Essential hypertension	Nifedipine, spironolactone, Teveten, valsartan
		Pulmonary hypertension	Orenitram
		<i>Endocrine</i>	
		Diabetes	Glipizide-metformin, rosiglitazone
		Fibrate	Fenofibrate, gemfibrozil
		<i>Neurology</i>	
		Pain	Aleve, Esbriet, Exalgo, Hysingla ER, ibuprofen, morphine
		Seizure	divalproex, Keppra
		<i>Psychiatry</i>	
		Antipsychotic	Risperidone
		Depression	Phenelzine, tranylcypromine, venlafaxine, Wellbutrin SR
		Stimulant	Benzphetamine, methylphenidate
		<i>Other</i>	
		Antibiotic	Amoxicillin, metronidazole
		Antihistamine	Famotidine
		Antineoplastic	Lysodren, Stivarga, Zytiga
		Contraceptive	Dasetta, Elinest, Falessa, Falmina, Juleber, Larin, Larin FE, Levonest, Loryna, Mono-Linyah, Northinodrone, Philith, Setlakin, Sharobel, Syeda, Tri-Linyah, Wera
		Decongestant	Zephrex-D
		Gallstone dissolution	Ursodiol
		Leukotriene antagonist	Montelukast
		Overactive bladder	Oxybutynin ER
	Capsule		
		Antiplatelet	Aspirin-dipyridamole
		Stool softener	DOK
		Proton pump inhibitor	Omeprazole
	Suspension		
		Antitussive	Delsym, Delsym ER, Tussionex
	Parenteral		
		Intravenous	
		Hemophilia	Recombinate, Hemofil M
		Antitrypsin deficiency	Aralast NP
		Subcutaneous	
		Cryopyrin-associated period syndromes	Arcalyst
	Topical		
		Ointment	
		Acne	Bensal HP
		Antibacterial	Mupirocin
		Anesthetic	Lidocaine
		Cream	
		Acne	Proactiv Clarifying Night acne treatment
		Antifungal	Ting, tolnaftate
		Steroid	Fluocinonide
		Gel	
		Anesthetic	Americaine, Astero, Astra-Dent, Benzocaine, Candee Caine, Comfortaine, Topex

(continued)

TABLE E2. (Continued)

Effective amount (strength)	Route of entry	Product group		Product examples
		Drug indication category	Condition treated	
		Lotion		
		Acne		Proactiv Gentle Formula Clarifying Night
		Solution		
		Antibacterial		Pre-Scrub II Surgical Hand Scrub
		Powder for reconstitution		
		Hemostatic agent		Recothrom
	Nasal	Solution		
		Decongestant		Oxymetazoline
		Steroid		Flunisolide, triamcinolone acetonide

FDA, US Food and Drug Administration; OTC, over-the-counter.

TABLE E3. FDA and OTC polysorbate 80-containing products

Effective amount (strength)	Route of entry	Product group Drug indication category Condition treated	Product examples
Grams	Parenteral	Intravenous	
		Immune globulin replacement	Gammagard S/D, Gammaplex, Bivigam
Milligrams	Parenteral	Subcutaneous	
		Immune globulin replacement	Hizentra
		Intra-articular	
		Steroid	Depo-Medrol
		Intramuscular	
		Contraceptive	Depo-Provera, medroxyprogesterone acetate
		Steroid	Depro-Medrol
Micrograms/Unknown	Oral	Intravenous	
		Cancer	Docetaxel
		Nausea	Emend
		Film-coated tablet	
		<i>Cardiovascular</i>	
		Angina	Betaxolol, carvedilol, Coreg, diltiazem, metoprolol succinate, metoprolol tartrate, verapamil
		Antiplatelet	Aspirin, dipyridamole
		Arrhythmia	Propafenone
		Essential hypertension	Benazepril, benazepril-hydrochlorothiazide, bisoprolol-hydrochlorothiazide, Caduet, felodipine, labetalol, methyldopa, spironolactone
		<i>Endocrine</i>	
		Diabetes	Glipizide, glyburide-metformin, metformin
		Fibrate	Fenofibrate, gemfibrozil
		Statin	Atorvastatin, Lipitor
		<i>Gastroenterology</i>	
		Nausea	Ondansetron
		IBS	Alosetron
		<i>Infectious diseases</i>	
		Antibiotic	Amoxicillin-clavulanate, cefuroxime, doxycycline, Levaquin, levofloxacin
		Hepatitis B	Epivir, Lamivudine
		HIV	Abacavir-lamivudine, Combivir, Epzicom, Kaletra, lamivudine-zidovudine, Norvir, Ziagen
		HSV	Valacyclovir, Valtrex
		Malaria	Chloroquine, hydroxychloroquine, Plaquenil, primaquine
		TB	Ethambutol
		<i>Neurology</i>	
		Migraine	Sumatriptan
		Muscle relaxer	Cyclobenzaprine
		Pain	Etodolac, fenoprofen, flurbiprofen, hydrocodone-ibuprofen, ibuprofen, morphine ER, nabumetone, Opana ER, oxaprozin, oxycodone ER, Oxycontin, propoxyphene-acetaminophen, tramadol, tramadol-acetaminophen, Ultracet, Ultram, Vicoprofen
		Parkinson's disease	Comtan, Entacapone
		Restless leg syndrome	Ropinirole
		Seizure	Divalproex, gabapentin, oxcarbazepine, Topamax
		<i>Oncology</i>	
		Aromatase inhibitor	Aromasin
		SERM	Evista, raloxifene
		<i>Psychiatry</i>	
		Alcohol/opioid dependence	Naltrexone
		Antipsychotic	Fluphenazine, perphenazine, prochlorperazine, quetiapine

(continued)

TABLE E3. (Continued)

Effective amount (strength)	Route of entry	Product group Drug indication category Condition treated	Product examples
		Depression	Amitriptyline, bupropion, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, paroxetine, Paxil, sertraline, Zoloft
		Insomnia	Ambien, eszopiclone, zolpidem
		<i>Rheumatology</i>	
		Gout	Probenecid
		Rheumatoid arthritis	Leflunomide
		<i>Other</i>	
		Antihistamine	Benadryl, cimetidine, cetirizine-pseudoephedrine, hydroxyzine, levocetirizine
		Overactive bladder	Oxybutynin
	Tablet		
		<i>Cardiovascular</i>	
		Angina	Carvedilol, bisoprolol, bystolic, metoprolol succinate
		Antiplatelet	Aspirin
		Essential hypertension	Eplerenone, Inspra, Lotensin, triamterene, triamterene-hydrochlorothiazide
		<i>Endocrine</i>	
		Diabetes	Fortamen
		Fibrate	Gemfibrozil
		Statin	Advicor
		<i>Infectious disease</i>	
		Antibiotic	Clarithromycin, doxycycline, levofloxacin, minocycline
		Hepatitis B	Lamivudine
		HSV	Valacyclovir
		Malaria	Hydroxychloroquine, mefloquine
		<i>Neurology</i>	
		Migraine	Sumatriptan
		Muscle relaxer	Cyclobenzaprine
		Pain	Diclofenac, IBU, ibuprofen, morphine ER, nabumetone, Opana ER, oxaprozin, Oxycontin, tramadol, Ultracet, Vimovo
		Seizure	Divalproex, gabapentin, levetiracetam, topiramate
		<i>Psychiatry</i>	
		Antipsychotic	Zyprexa, prochlorperazine
		Depression	Bupropion SR, citalopram, escitalopram, paroxetine, sertraline, venlafaxine ER
		<i>Other</i>	
		Antihistamine	Cimetidine, hydroxyzine
		Contraceptive	Apri, Caziant, Gianvi, Jolessa, Loseasonique, Mononessa, Ortho Tri Cyclen Lo, Rajani, Reclipsen, Seasonique, Trinessa, Velivet Triphasic
		Decongestant	Sinus congestion
		Overactive bladder	Oxybutynin, Ditropan XL
		Proton pump inhibitor	Pantoprazole, Prilosec, Protonix
		SERM	Evista, raloxifene
	Capsule		
		<i>Cardiovascular</i>	
		Angina	Diltiazem ER
		Essential hypertension	Amlodipine-benazepril, Dyazide, Lotrel, triamterene-hydrochlorothiazide
		<i>Gastroenterology</i>	
		Proton pump inhibitor	Dexilant, esomeprazole, Kapidex, lansoprazole, Nexium, omeprazole, Prevacid
		Stool softener	Natural Daily Fiber

(continued)

TABLE E3. (Continued)

Effective amount (strength)	Route of entry	Product group Drug indication category Condition treated	Product examples
		<i>Other</i>	
		Antibiotic	Doxycycline, Oracea
		Antihistamine	Diphenhydramine, loratadine
		BPH	Tamsulosin
		Depression	Duloxetine, fluoxetine
		Steroid	Entocort, budesonide
		Pain	Indomethacin, tramadol
		Vitamin	Ergocalciferol
		Weight loss	Phentermine
		Powder for solution	
		Antibiotic	Amoxicillin-clavulanate, cefadroxil, erythromycin-sulfisoxazole, cholestyramine
		Bile acid sequestrant	
		Suspension	
		Antibiotic	Sulfamethoxazole-trimethoprim
		Antitussive	Delsym, hydrocodone-chlorpheniramine
		Asthma	Budesonide, Pulmicort
		Pain	Ibuprofen
	Parenteral	Intra-articular	
		Steroid	Kenalog-10, Kenalog-40
		Intramuscular	
		Vaccine	Boostrix, Fluad, Fluarix Quad, Flulaval Quad, Flucelvax Quad, Gardasil, Gardasil 9, Heplisav-B, Infanrix, Kinrix, Pediarix, Pentacel, Prevnar 13, Quadracel, RotaTeq, Shingrix, Trumenba
		Intravenous	
		Arrhythmia	Amiodarone
		Neutropenia	Neupogen
		Vaccinia	CNJ-016
		Vitamin	Phytonadione
		Subcutaneous	
		Neutropenia	Neupogen
	Topical	Gel	
		Acne	Epiduo, Finacea
		Anesthetic	Lidocaine
		Antifungal	Naftin
		Lotion	
		Lice	Ulesfia, Sklice
		Sunscreen	All day moisture
		Cream	
		Acne	Salicylic acid
		Antifungal	Terconazole, ketoconazole, terpenicol
		Solution	
		Antibacterial/steroid, otic	Cortisporin-TC, neomycin-polymyxin B-dexamethasone, neomycin-polymyxin B-hydrocortisone
		Pain, ophthalmic	Bromday, bromfenac
		Steroid, ophthalmic	Dexamethasone sodium phosphate, Durezol, prednisolone acetate
		Patch	
		Pain	Flector, Hot and Cold Medicated Patch, Medrox, Mencaine, Terocin

(continued)

TABLE E3. (Continued)

Effective amount (strength)	Route of entry	Product group Drug indication category Condition treated	Product examples
		Paste	
		Dental	Crest Sensitivity Whitening Plus Scope, Crest 3D White
	Nasal	Solution	
		Osteoporosis	Fortical
		Steroid	Beconase, Children's Rhinocort Allergy, fluticasone propionate, mometasone furoate, Nasonex, triamcinolone acetonide, Veramyst

BPH, Benign prostatic hypertrophy; FDA, US Food and Drug Administration; HSV, herpes simplex virus; IBS, irritable bowel syndrome; OTC, over-the-counter; SERM, selective estrogen receptor modulators.

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