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REVIEW

Immediate-type hypersensitivity to polyethylene glycols: a review

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Summary
Polyethylene glycols (PEGs) or macrogols are polyether compounds widely used in medical and household products. Although generally considered biologically inert, cases of mild to life-threatening immediate-type PEG hypersensitivity are reported with increasing frequency. Nevertheless, awareness of PEG's allergenic potential remains low, due to a general lack of suspicion towards excipients and insufficient product labelling. Information on immediate-type reactions to PEG is limited to anecdotal reports, and the potential for PEG sensitization and cross-sensitization to PEGylated drugs and structurally related derivatives is likely underestimated. Most healthcare professionals have no knowledge of PEG and thus do not suspect PEG's as culprit agents in hypersensitivity reactions. In consequence, patients are at risk of misdiagnosis and commonly present with a history of repeated, severe reactions to a range of unrelated products in hospital and at home. Increased awareness of PEG prevalence, PEG hypersensitivity, and improved access to PEG allergy testing, should facilitate earlier diagnosis and reduce the risk of inadvertent re-exposure. This first comprehensive review provides practical information for allergists and other healthcare professionals by describing the clinical picture of 37 reported cases of PEG hypersensitivity since 1977, summarizing instances where PEG hypersensitivity should be considered and proposing an algorithm for diagnostic management.

Introduction

Polyethylene glycols (PEGs) or macrogols comprise a family of hydrophilic polymers widely used in medical, pharmaceutical, cosmetic, industrial and food products. Exposure extends from the household to perioperative setting, and PEGs are common constituents of a variety of products including wound dressings, PEGylated drugs and hydrogels as well as tablets, lubricants and dental floss [1, 2]. The polymer group has since its development held a reputation for safety and utility [2, 3]. Since 1990 however, mild to life-threatening immediate-type hypersensitivity reactions (HSRs) to PEGs have been increasingly reported. Nonetheless, due to a lack of suspicion towards excipients, non-standardization of ingredient nomenclature and inadequate product labelling, awareness of PEGs and their allergenic potential remains minimal. Accordingly, patients are at risk of repeated life-threatening reactions due to misdiagnosis. No studies to date examine the prevalence of PEG hypersensitivity, although occurrence is likely underestimated. Information regarding patient management and comprehensive review of immediate-type PEG hypersensitivity is at present lacking from the literature.

Objective

The objective of this study is to provide information of practical use to the allergist and general physician by reviewing the literature on immediate-type PEG hypersensitivity.

Literature search

A literature search was conducted in PubMed, SciVerse and EMBASE entering queries for 'hypersensitivity', 'allergy', 'allergic', 'anaphylaxis', 'anaphylactic', 'urticaria' or 'angioedema' in association with the terms, 'polyethylene glycol', 'PEG' or 'macrogol'. Inclusion criteria were articles published between January 1977 and April 2016, describing PEG-attributed immediate-type HSRs comprising: anaphylaxis with respiratory and circulatory symptoms, cutaneous manifestations and/or angioedema in individuals of all ages. Relevant bibliographical references from identified reports were

reviewed. In addition, standard textbooks on PEGs were consulted. Although briefly discussed, review of delayed-type PEG hypersensitivity was deemed beyond the scope of this study.

Background on polyethylene glycols

Molecular structure

Polyethylene glycols ($H(OCH_2CH_2)_nOH$) are synthesized via polymerization of ethylene oxide (Fig. 1). Resulting PEG polymers vary in chain length and molecular weight (MW) within a narrow distribution [4]. PEGs are typically uncharged and may be linear or branched. In addition, PEGs can be methylether-capped (MPEGs or PEG MME), thereby reacting only at one terminal [5].

PEG nomenclature

Polyethylene glycols have numerous synonyms, the most common of which are listed in Table 1. Differing PEG nomenclatures exist, rendering identification and avoidance challenging. The term 'PEG' is most often used in combination with a numerical value. In the cosmetic industry, the number refers to the average number of ethylene oxide units (n) in each molecule [i.e. PEG 75 (where $n = 75$)]. In the pharmaceutical industry, the number denotes the rounded, average MW (g/mol) of a given PEG product [i.e. PEG 3350 (g/mol)] (i.e. $75 \times 44 \approx 3350$). Thus, the same compound may be named PEG 3350 or PEG 75 depending on the product type in which it figures.

Molecular weight and physical properties

Commercially available MWs range from 200 to 35 000 g/mol [5]. As the MW of ethylene oxide is 44, a given PEG product's MW may be roughly calculated as $n \times 44$, where n is the number of repeating units (Fig. 1). PEGs of low MW (<400 g/mol) are clear, viscous liquids, while high MW (>1000 g/mol) are opaque solids or powders. Physiological absorption and thus toxicity decreases with increasing MW: PEGs under 400 g/mol are readily absorbed through intact gastrointestinal mucosa [6], compared with <10% for PEG 3300 g/mol and <2% for higher MWs [7, 8]. Similarly, only PEGs with MW under approx. 3350 g/mol are absorbed through intact skin [9] and low MWs are known to enhance cutaneous penetration and bioavailability of other chemicals [10].

Table 1. Synonyms for polyethylene glycol (PEG)-based compounds

CAS number: 25322-68-3		
Alkox®	MiraLax®	Polikol
Carbowax™	Oxyethylene polymer	Polyox
Ethylene Glycol polymer	Polyethylene oxide	Polyoxyethylene diol
Ethylene Oxide polymer	Polygol	Polyoxyethylene ether (POE)
Kleanprep®	Polyoxirane	Poly(oxy-1,2-ethanediyl)
Macrogol	Pluriol	

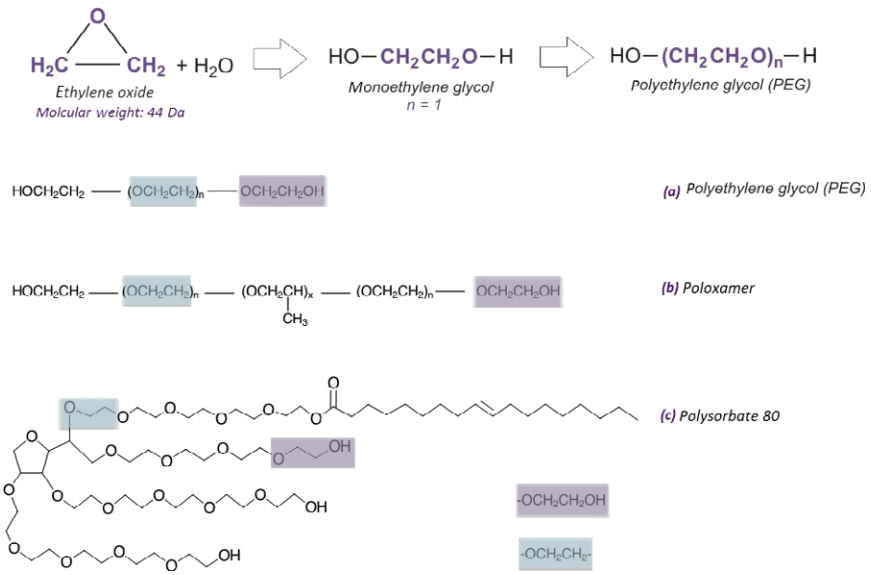

Fig. 1. Polymerization and molecular structure of polyethylene glycol (PEG) and PEG derivatives. Two chemical moieties, $-(OCH_2CH_2)-$ and $-OCH_2CH_2OH$, are shared by both PEGs and some PEG derivatives, making cross-sensitization theoretically possible [29].

Applications of PEGs

Polyethylene glycol's range of physicochemical properties and marked toxicological safety render them suited for a variety of applications [3, 4]. The most widely used of the glycols in the pharmaceutical industry [11], PEGs serve as active ingredients of laxatives and bowel preparations. Still more frequently, PEGs are used as excipients and figure ubiquitously in pill binders, tablet surface coatings, parenteral liquid preparations, lubricants, ultrasound gels, ointment bases, suppositories and organ preservatives [5]. Due to their water-binding properties, PEGs are also found in medical materials such as wound dressings, hydrogels, orthopaedic bone- and neurosurgical dural sealants. Recently, PEGs have been employed in polymer-based drug delivery. Termed PEGylation, PEGs are covalently attached to systemic drugs to increase MW, prolong circulation time and shield the drug from the immune system by preventing opsonization. PEGylated drugs are common in cancer, gout and immunotherapies [12].

In the cosmetic and fragrance industry, PEGs are widespread in salves, creams, lotions, shampoos, hair gels, hair dyes, lipsticks, shaving creams and oral hygiene products [13]. PEGs also figure as food additives and are prevalent in the textile, paper, leather, plastic, ceramic, metal and chemical industry [2].

PEG derivatives: structurally related polymers

Structurally similar PEG derivatives include PEG ethers (i.e. PEG laureths, ceteths, ceteareths, oleths), PEG fatty acid esters (i.e. PEG laurates, dilaurates, stearates and distearates), PEG amine ethers, PEG castor oils (BASF Corp, Ludwigshafen, Germany), PEG–propylene glycol copolymers (poloxamers), PEG sorbitans (polysorbates) and PEG soy sterols (Fig. 1) [2]. PEG derivatives share structural similarities with PEGs, and are similarly common excipients in cosmetic and pharmaceutical products. Nomenclature follows that of the cosmetic industry.

Literature review of immediate-type hypersensitivity to PEGs

In total, 37 case reports of immediate-type hypersensitivity to PEGs published between January 1977 and April 2016 were identified. Table 2 summarizes each case, including information on age, gender, HSR symptoms, causal agent and results of allergy investigation. Approximately 74 reactions were recorded in 37 patients. Fourteen patients were women, 23 were men. The mean age was 47 (range 24–86). No reactions were reported in children.

Clinical presentation

Symptoms associated with immediate-type PEG hypersensitivity were often severe and rapid in onset. Of the 37 cases identified, 28 (76%) described HSRs that fulfilled criteria for anaphylaxis [8, 14–40]. Common manifestations were pruritus, tingling, flushing, urticaria, angioedema, hypotension and bronchospasm. Symptoms typically appeared within minutes following PEG exposure, with many cases describing near-instant localized itching or discomfort at the site of application, followed by systemic symptoms. In 11 (30%) cases, HSRs of both severe and mild character were reported in the same patient.

Exposure route

A multitude of exposure routes are described in the literature. Thirty (81%) cases were linked to per oral exposure, two occurred perioperatively, one via vaginal mucosa and six (16%) followed intra-articular, intramuscular or intravenous injection; usually of steroid depot formulations. All cases describing injection of PEG-containing products or perioperative PEG exposure developed anaphylaxis. In comparison, 24 (36%) of per oral exposures reported an anaphylactic outcome. Despite significant prevalence in topical products, only ten (27%) cases reported HSRs following cutaneous PEG exposure, at least three of which were on broken skin, causing wheezing, pruritus, urticaria and oedema [16, 25–27, 29, 39, 41–43]. In contrast to injection and per oral exposures, no cases of topical administration were linked to anaphylaxis. HSR severity may depend on PEG dose available for absorption: low MW PEGs show limited absorption in healthy skin and PEGs >4000 g/mol are not absorbed at all [2]. For this reason, topical application of higher MW PEGs, particularly on intact skin, appears less likely to cause reactions in sensitized individuals.

In ten (27%) cases, patients developed HSRs via more than one form of exposure [14, 16, 19, 21, 25–27, 29, 39, 43]. Thus, when administered in sufficient dose, immediate-type PEG hypersensitivity may be provoked via multiple exposure routes.

Reaction threshold dose

Patient history and oral challenge findings imply that PEG dose may be a critical factor in eliciting a HSR. In a PEG 4000-hypersensitive patient who underwent graded oral challenge starting with 1 mg and increasing dose every 30 min, a positive systemic response was first observed 30 min following ingestion of 7.1 g PEG 4000 (equivalent to the minimal dose in many bowel

Table 2. Immediate-type hypersensitivity reactions to polyethylene glycols (PEGs) reported in the literature from 1977 to 2016

Age	Sex	Exposure	Immediate-type reaction	PEG skin test results	Other test results	Reference
27	F	Intramuscular Depo-medrol® injection (PEG 3350)	Anaphylaxis: Immediate onset facial erythema pruritus, dizziness, hoarseness, vomiting.	Prick test: positive for undiluted DepoMedrol (PEG 3350), Carbamid skin cream (PEG 1500), Helosan skin cream (PEG 100-stearate), chewable Balancid novum tablet (PEG 6000) and PEG 3350 10% PEG 6000 100%.	Direct and Indirect basophil histamine release test: positive for Balancid Novum tablet suspension (PEG 6000), PEG 3350 10% and PEG 6000 100% Negative histamine release test for ethylene glycol (monomer) 100% and diethylene glycol (dimer) 100%. Oral provocation with Telfast® antihistamine (PEG 400 in tablet film) negative after 2 tablets	[27]
		Balancid Novum® reflux tablet (PEG 6000)	Anaphylaxis: Immediate palmo-plantar pruritus, urticaria, vomiting			
		Effexor® antidepressant tablet (PEG 400)	Generalized pruritus			
		Helosan® cream (PEG 100-stearate)	Localized pruritus	Negative prick test for ethylene glycol 100% (monomer), diethylene glycol 100% (dimer) and polysorbate 80 20%		
69	M	Unidentified perioperative exposure during evacuation of subdural haematoma	Anaphylaxis: hypotension, generalized urticaria and pruritus 60 min after induction.	Prick test: positive for PEG 6000 50%, PEG 3000 50%, polysorbate 80 20%, Chlorhexidine solution containing polysorbate 80 and Mepilex bandage. Negative prick test for PEG 300 100%, ethylene glycol 100%, diethylene glycol 100% and Chlorhexidine solution not containing polysorbate 80	Negative histamine release test for PEG 3000 and 6000 at 100%	[26]
		Deprakine Retard® antiepileptic (PEG 3000, PEG 3500)	Anaphylaxis: hypotension, generalized erythema and pruritus within minutes.			
		Grepid® anticoagulant (PEG 6000)	Anaphylaxis: hypotension, generalized erythema and pruritus after 6–8 h.			
		Mepilex® bandage (PEG-containing film)	Generalized pruritus, urticaria, sneezing within an hour.			
		Chlorhexidine 0.5% (polysorbate 80)	Anaphylaxis: hypotension, generalized erythema within minutes			
26	F	Antibiotic tablets (PEG-containing amoxicillin clavulanate & ciprofloxacin)	Multiple episodes of generalized urticaria 1 h after ingestion	Prick test: positive for ciprofloxacin 0.001% (containing unspecified PEG), PEG 400 0.001%, 4000 0.001%, 6000 0.01% and polysorbate 80 0.001%. Negative prick test for non-PEG containing	Oral provocation with 45 mg PEG-containing amoxicillin clavulanate induced diffuse urticaria after 30 min. PEG-containing meloxicam, imidazole salicylate and etoricoxib caused diffuse urticaria shortly after ingestion of small doses. Oral provocation with non-PEG-containing etoricoxib, amoxicillin clavulanate and ciprofloxacin: negative Negative basophil activation test (BAT) for PEG 400, 4000 and 6000 (unspecified concentration). Specific IgE for ethylene oxide, benzylpenicillin, ampicillin and amoxicillin negative	[39]
		Anti-inflammatory drugs (PEG-containing ketoprofen granules & diclofenac)	Multiple episodes of generalized urticaria 1 h after ingestion			
		Cosmetics (containing PEG)	Urticarial reactions			

(continued)

Table 2 (continued)

Age	Sex	Exposure	Immediate-type reaction	PEG skin test results	Other test results	Reference
33	M	Povidone–iodine gel (PEG 400, PEG 4000 and PEG 6000) applied to 'dead space' resulting from lumbar disc surgery.	Anaphylactic shock after a few minutes.	Prick test: positive to PEG 6000 0.01%, POEPOPG 0.01%, polysorbate 80 0.1% and hydroxyethylated starch 0.01%. Negative prick test for PEG 400 1% and PEG 4000 1%	None	[29]
		Shampoo (polyethylene–polypropylene glycol (POEPOPG) and polysorbate 80)	Wheezing			
		Hespander® plasma expander infusion. (Hydroxyethylated starch)	Anaphylaxis			
54	F	Intra-articular injection of DepoMedrol® Lidocaine (PEG 3350)	Anaphylaxis: respiratory distress, generalized erythema, pruritus, hypotension after a few minutes	Prick test: positive for PEG 3350 at 10% and 100% solution. Negative prick test for PEG 3350 at 0.01, 0.1% and 1%. Intradermal testing: positive for PEG 3350 1%. 10% PEG 3350 showed anaphylaxis within 10 min of injection	Negative basophil activation test (BAT) for PEG 3350	[28]
46	M	Nimesulide DOC® granules (PEG 4000)	Urticaria and itch of the mouth within minutes of ingestion.	Prick Test: positive for PEG 4000 0.0001%, PEG 6000 0.0001% and Paracetamol syrup (PEG 6000) 50%. Negative prick test for PEG 400 50%. Patch test for unspecified PEG: negative	CD203 basophil activation test positive for PEG 4000 and 6000 at 1:100 000 dilution, negative for PEG 400 at all dilutions. Negative specific IgE ethylene oxide	[15]
		Paracetamol syrup (PEG 6000)	Rapid generalized urticaria, angioedema, dyspnoea			
55	M	SELG® lavage solution (PEG 4000)	Sneezing, rhinorrhoea, urticaria after several min.	Prick Test: positive for PEG 4000 0.1% Negative prick test for PEG 4000 0.01% and 0.001%	Oral provocation with nimesulide not containing ceto-macrogol: negative	[30]
		Lovol esse® lavage solution (PEG 4000)	Anaphylaxis: throat closure, chest tightness, dyspnoea, face erythema and near fainting after 10 min.			
		Mesulid® nimesulide soft capsule (cetomacrogol 1000)	Generalized urticaria			
52	M	PEG 3350 lavage solution	Anaphylaxis: flushing, urticaria, wheezing, tachycardia, hypotension, unconsciousness within minutes.	Prick Test: positive for PEG 9000 0.001%, PEG 3350 0.01%, PEG 1000 100% and PEG 200 100%	None	[25]
		Unspecified sunscreen containing PEG	Pruritic maculopapular rash within minutes of application.			
		Unspecified toothpaste containing PEG	Lip swelling			

(continued)

Table 2 (continued)

Age	Sex	Exposure	Immediate-type reaction	PEG skin test results	Other test results	Reference
		Naproxen tablet containing PEG	Pruritus, dyspnoea, urticaria within minutes of ingestion			
57	F	Laxative Colopeg® (PEG 3350)	Anaphylaxis: palmar pruritus, dizziness, generalized urticaria, hypotension after 10 min	Prick Test: positive for Colopeg (PEG 3350) 100% and undiluted Pegylated Interferon-α2a	None	[23]
36	M	Bohm® evacuant solution (PEG 4000)	Urticaria and angioedema	Prick test: negative for Bohm solution and PEG 4000 0.1% Intradermal test: positive for PEG 4000 0.1% showing urticaria, rhinitis, nausea and vomiting.	Oral provocation with 25 cc PEG 4000: generalized urticaria, rhinitis, nausea, vomiting after 5 min.	[63]
44	M	Bohm® evacuant solution (PEG 4000)	Urticaria and angioedema	Prick test: negative for Bohm solution and PEG 4000 (unspecified concentrations). Intradermal test: positive for PEG 4000 0.0001% Patch test for Bohm solution and PEG 4000: negative	Oral provocation with PEG 4000 and Bohm solution: positive	[63]
44	F	Depo-Medrol® lidocaine intra-articular injection (PEG 3350)	Anaphylaxis: generalized urticaria, bronchospasm, hypotension after 10 min	Prick test: positive for Depo-Medrol lidocaine and PEG 4000 0.1% Negative prick test for PEG 1500 and 300 at 100%.	Oral provocation with increasing concentrations of PEG 4000: anaphylaxis at 7.1 g with palmar pruritus, oedema of lips, eyelids, feet and hands	[31]
68	M	Imposit® throat lozenge (PEG 8000)	Oral burning within minutes of ingestion leading to anaphylaxis: hypotension, tachycardia, urticaria.	Prick test: positive for PEG 4000 1% and spreading urticaria and cough with PEG 8000 1%.	Significant levels of PEG-specific IgE not identified No C4 or C3 complement consuming reaction could not be identified	[17]
		Ledermix-Paste® dental paste (PEG 3000 and 400)	Oral burning and severe pain	Negative prick test for PEG 3000 1% and 400 (unspecified concentration)		
58	M	Citrate de betaine UPSA® effervescent tablet (PEG 6000)	Anaphylaxis 30 min after ingestion.	Prick test: positive for PEG 1500, 300, Florax (PEG 4000) and Aetoxisclerol (lauromacrogol 400)	None	[19]
		Betneval® corticosteroid cream (cetomacrogol 1000)	Immediate contact urticaria	(unspecified concentration)		
		Nerisone® cream (PEG 2000 stearate)	Immediate contact urticaria			
		Penglobe® (PEG 6000)	Maculopapular exanthema			
36	M	V-Pen® mega antibiotic (PEG 6000)	Anaphylaxis: generalized urticaria, dizziness, tachycardia within a few minutes.	Prick test: positive for Fludent, Bafucin and PEG 6000 (unspecified concentration)	In vitro studies of specific IgE to PEG 6000 inconclusive as control serum demonstrated similar binding in immunospot	[14]
		Fludent® flouride tablet (PEG 6000)	Urticaria			

(continued)

Table 2 (continued)

Age	Sex	Exposure	Immediate-type reaction	PEG skin test results	Other test results	Reference
		Bafucin® throat lozenge (PEG 6000)	Urticaria			
24	F	Fludent® flouride tablet (PEG 6000)	Anaphylaxis: immediate onset angioedema,dizziness, urticaria, hypotonia.	Prick test: positive for Fludent, PEG 6000 and Aqualan L cream. (unspecified concentration)	None	[14]
		Aqualan L® emollient cream (ceto-macrogol)	Urticaria			
45	M	Intra-articular injection of Diprostene® (PEG 4000)	Anaphylaxis: nasal pruritus, conjunctivitis, dizziness, tongue oedema, dyspnoea, generalized urticaria within 2 min	Prick test: positive for PEG 4000 (unspecified concentration). Intradermal test: positive for PEG 4000 at 0.001%, provoking facial erythema and periorbital oedema	None	[20]
42	F	Dentifrice A® dental paste (PEG 5000 and polyoxyethylene–polyoxypyrene glycol POEPOPG)	Anaphylaxis: immediate oral discomfort, generalized erythema and dyspnoea	Prick test: positive for Dentifrice A 0.1%, unspecified concentration of POEPOPG, PEG 20 000 0.01%, PEG 6000 0.01% and PEG 4000 0.01%. Negative prick tests for PEG 1500, PEG 400, Dentifrice B (PEG 400) and Dentifrice C (PEG 600) (unspecified concentration)	None	[34]
41	F	Chester Packaging Ultrasound Gel® (PEG 8000)	Anaphylaxis: within minutes intra- and perivaginal pruritus and burning. Over several hours, labial swelling, flushing, throat tightness, dyspnoea, nasal congestion and generalized urticaria	Prick test: positive for ultrasound gel (PEG 8000) and PEG 8000 (unspecified concentration) Negative prick tests for latex and non-latex condom	Specific serum IgE negative for latex	[40]
		Unspecified ultrasound gel	Anaphylaxis: local vaginal pruritus followed by periorbital and lingual oedema, urticaria, cough, dyspnoea			
44	F	Golytely® lavage solution (PEG 3350) at laxative doses	Anaphylaxis: unconsciousness, seizures	Prick test: positive for PEG 3350 (unspecified concentration).	None	[21]
		Depo-Medrol corticosteroid injection (PEG 3350)	Anaphylaxis: unconsciousness, angioedema, flushing, dyspnoea			
36	M	Multivitamin tablet (PEG 20 000 and PEG 8000)	Anaphylaxis: hypotension, unconsciousness, seizures.	Prick test: positive to PEG 20 000 and PEG 8000 0.1%	None	[16]
		Unspecified drugs, aftershaves and lotions	Four episodes of anaphylaxis with unknown aetiology and recurrent urticaria			

(continued)

Table 2 (continued)

Age	Sex	Exposure	Immediate-type reaction	PEG skin test results	Other test results	Reference
47	M	Paint (PEG 4000)	Generalized urticaria within 10–15 min.	Prick test: negative for PEG 4000 100%.	None	[43]
		Bohm® evacuant solution (PEG 4000)	Lip swelling and generalized urticaria within 15–20 min on two separate occasions.	Intradermal test: negative PEG 4000 at 0.1% and 0.01%. Patch test: negative for PEG 4000		
		Paint (PEG 4000)	Lip swelling and generalized urticaria within 15–20 min			
35	F	Americaine Otic® Topical solution (PEG 300)	Immediate pruritus and exacerbation of chronic otitis externa	Rubbing PEG 300 on patient's forearms produced urticarial reactions within 20 min. Patch test: negative to Americaine Otis (PEG 300) and PEG 300 (unspecified concentration).	None	[42]
50	M	Topical Lotrimin cream (PEG 400) to fungal infection.	Pruritus, erythema and exanthem within 15 min of application.	Open test: rubbing Lotrimin, Tinactin and PEG 400 on patient's forearms produced weal and flare urticarial reactions.	None	[41]
		Topical Tinactin solution (PEG 400)	Pruritus, erythema and exanthem within 15 min of application			
		Furacin® soluble dressing (PEG 4000, 1000 and 300) on skin burn	Pruritus and superimposed dermatitis	Patch test: negative to Lotrimin (PEG 400), Tinactin (PEG 400) and PEG 400 (unspecified concentration)		
30	F	Golytely® lavage solution (PEG 3350)	Anaphylaxis: throat itch, generalized pruritus and erythema, chest tightness and urticaria within minutes	None	None	[8]
74	M	Halflytely® lavage solution (PEG 3350)	Anaphylaxis: Throat tingling, choking sensation, hoarseness, tongue swelling, hypotension	None	None	[32]
39	M	Colyte® lavage solution (PEG 3350)	Anaphylaxis: Generalized urticaria, itching, dizziness, dysphagia, tingling arms and legs, dyspnoea and severe hypotension after 5 min	None	None	[33]
33	F	Unspecified PEG lavage solution	Anaphylaxis: urticaria, dyspnoea, chest tightness, angioedema, dizziness, tongue swelling	None	None	[24]
52	F	Golytely® lavage solution (PEG 3350)	Anaphylaxis: perioral angioedema, pain, pruritus, dyspnoea	None	None	[35]
46	M	Colonoscopy solution (PEG 3350)	Urticaria	None	None	[71]
70	M	Golytely® lavage solution (PEG 3350)	Oral tingling after 20 min followed by tongue swelling, angioedema, oedema of lower extremity	None	None	[72]

(continued)

Table 2 (continued)

Age	Sex	Exposure	Immediate-type reaction	PEG skin test results	Other test results	Reference
86	F	Golytely® lavage solution (PEG 3350)	Generalized urticaria and pruritus	None	None	[73]
70	M	Golytely® lavage solution (PEG 3350)	Anaphylaxis: hypotension, erythema, wheezing	None	None	[18]
42	M	Fortrans® lavage solution (PEG 4000)	Asthma and urticaria	None	None	[36]
52	M	Klean-Prep® lavage solution (PEG 4000)	Asthma and bronchospasm and cardiovascular collapse	None	None	[37]
42	M	Klean-Prep® lavage solution (PEG 4000)	Vomiting, urticaria, coughing	None	None	[38]
32	M	Klean-Prep® lavage solution (PEG 4000)	Allergic exanthem	None	None	[74]
		Colopeg® lavage solution (PEG 3350)	Generalized urticaria			

preparations) [31]. This delay may be attributed to dose threshold and/or PEG absorption rate. A patient with skin prick test (SPT)-confirmed hypersensitivity to PEG 3350 and 6000 showed no response during oral challenge with Telfast® (Sanofi-Aventis, Hørsholm, Denmark) – an antihistamine with PEG 400 only in the tablet coating. Authors interpret this to suggest that dose and/or MW were too low to elicit a response [27].

Unfortunately, while MWs are usually displayed, PEG concentrations are almost never made available on ingredient labels. Determining the minimum concentration likely to provoke responses by various exposure routes is thus not straightforward. Instances where PEGs figure in low concentrations, for example in tablet coatings, illustrate the practical dilemma in determining what products a sensitized patient may tolerate. Based on the reviewed cases, it is likely that patients have an individual reactivity-threshold for both dose and MW.

Product source

Bowel preparations or laxative solutions were described as culprit agents in 20 cases (54%). Despite a reported gastrointestinal mucosal absorption rate significantly under 1% for the 3350 g/mol PEG product common to bowel preparations [35], 14 cases reported severe anaphylactic reactions. The predominance of bowel preparation-associated HSRs may have multiple explanations: i) as the active ingredient in bowel preparations, PEGs are easily implicated; ii) bowel preparations contain uniquely high concentrations of PEG, increasing the likelihood of surpassing an individual's threshold dose; and iii) bowel preparations are frequently used in connection with colonoscopy, often indicated in instances of inflammation and/or damaged gastrointestinal mucosa. It is thus possible that compromised mucosa may increase absorption of high MW PEGs [8, 44, 45] and predispose to PEG sensitization. Accordingly, in at least two cases, authors conclude that a loss of mucosal integrity caused by gastrointestinal disease may have led to increased PEG absorption [8, 25].

A history of *repeated* HSRs caused by a *range* of PEG-containing products was recorded in 16 cases (43%). In addition to bowel preparations, a variety of prescription, over-the-counter, medical, household and industrial products feature in the cases reviewed. Culprit products include corticosteroid formulations, vitamin/mineral preparations, throat lozenges, ultrasound gels, disinfectants, antiepileptics, antiemetics, anticoagulants, antidepressants, analgesics, antibiotics, anti-inflammatory drugs and reflux medication as well as toothpaste, dental floss, pharmaceutical and cosmetic creams, shampoos and paint. Products based on novel, (PEG)-based polymer technology including advanced wound

dressings, tissue sealants and hydrogels have in recent cases also been implicated [26]. Hence, when dealing with a patient suspected of PEG hypersensitivity, a history of adverse reactions to *any* product type should be addressed and a high index of suspicion is warranted in patients with several severe reactions to seemingly unrelated products. As PEG and other excipient content varies between drug brand names and dosages, it is imperative that the *exact* product to induce HSR be tested, ensuring examination not only of active ingredient, but excipients within the particular formulation.

PEGs are used extensively in the perioperative environment, including in products often not noted on charts [26]. PEGs and derivatives should thus be considered when investigating perioperative HSRs. Table 3 summarizes instances where allergy investigation for PEG hypersensitivity may be appropriate.

Table 3. Patients for which polyethylene glycol (PEG) allergy testing should be considered

Patients with HSRs to PEG-containing products where sensitization to active ingredients has been excluded
Patients with HSRs to PEG-containing bowel preparations
Patients with repeated HSRs to unrelated drugs and products (sometimes labelled 'idiopathic anaphylaxis')
Patients with HSRs to only certain brand names or doses of the same drug
Patients with HSRs to PEGylated drugs where hypersensitivity to the active drug is excluded
Patients with HSRs following invasive procedures or perioperative HSR
Patients with HSRs to a PEG derivative

HSR, hypersensitivity reaction; PEG, Polyethylene glycols.

Notably, no cases of HSRs to PEGs in food products have been reported. However, as a case of immediate-type hypersensitivity to the PEG-derivative polysorbate 80 in ice cream is described [46], the risk of food-associated PEG hypersensitivity cannot be fully dismissed.

Molecular weight

The distribution of MW in the reported cases is shown in Fig. 2. The most common MWs in bowel preparations, PEG 3350 and 4000 represented 28 (55%) of the 51 individual immediate-type HSRs where MW was specified. Products containing PEG 6000 were linked to 10 (20%) HSRs. Other MWs to cause HSRs included PEG 300, 400, 1000, 3000, 3500, 5000, 8000 and 20 000.

Reactivity and positive SPTs to multiple MWs was a shared feature of numerous cases [15–17, 19, 25–27, 31, 34, 39]. In some SPT studies, reactivity was limited to high MW PEGs ≥4000 [15, 17, 31, 34]. However, cases of hypersensitivity to both low and high MWs were also described [19, 25, 27, 39]. Interestingly in all cases, the PEG of highest MW to be examined always showed a positive SPT. This may suggest the absence of an upper limit for MW in regard to reactivity.

It can be speculated that MW is important both in the process of sensitization and in HSR severity. Low MWs penetrate skin and mucosa to a greater degree, increasing the risk of sensitization. Once sensitized

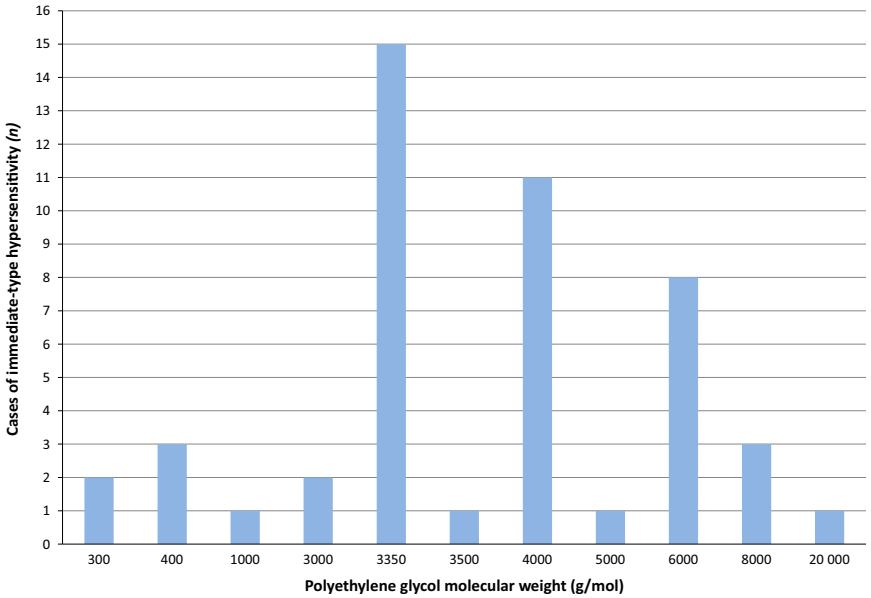

Fig. 2. Frequency of immediate-type hypersensitivity reactions to polyethylene glycol (PEG) by molecular weight.

however, provided that immediate-type hypersensitivity to PEGs is IgE-mediated, high MW PEGs could demonstrate greater multivalence, requiring lower concentrations to show a response. Shah et al. [25] found evidence to support this theory, reporting SPT to 1:1000 dilution of PEG 9000 and only to full concentration PEG 3350. Also, positive SPT results to PEG 1000 and 200 necessitated higher concentrations, presented smaller weal/flare and were slower to develop. A patient described by Hesselbach et al. [17] showed similar proportionality between MW and response: SPT with 1% PEG 8000 produced cough, urticaria and a large weal/flare response, 1% PEG 4000 provoked a local, smaller weal/flare while 1% PEG 3000 was negative. More recently, Yamasuji et al. [29] reported negative prick test results to 1% PEG 400 and 1% PEG 4000 in a patient with SPT-confirmed allergy to 0.01% PEG 6000. In basophil activation tests (BAT) performed by Bommarito et al. [15], PEG 4000 and PEG 6000 at 0.0001% showed positive response, while PEG 400 in any dilution did not. Combined, these findings indicate a need for testing numerous MWs when investigating suspected immediate-type PEG hypersensitivity. Importantly, in addition to the MW in the offending product, PEGs >3000 g/mol should be tested before hypersensitivity may be excluded. SPT with lower MW PEGs may require comparatively greater test concentrations to show a response.

Hypersensitivity to structurally related polymers and PEGylated drugs

Although only sporadically examined, immediate-type cases of sensitization to PEG derivatives are described, with polysorbates (Tweens), poloxamers, PEG castor oils (Cremophor ELBASF Corp, Ludwigshafen, Germany) and laureth-9 (polidocanol) implicated in HSRs [22, 39, 47–53]. Importantly, some evidence suggests the potential for cross-reactivity between these structurally related polymers and PEG (Fig. 1). In a report by Hyry et al. [14], a patient with anaphylaxis following PEG 6000 ingestion developed contact urticaria to a cream containing the PEG-derivative cetomacrogol; reactivity was later confirmed in SPT. Co-Minh et al. [19] described a case of immediate HSR to PEG, PEG 40 stearate, cetomacrogol 1000 and positive SPTs to Aetoxysclerol (Kreuss ler Pharma, Roissy-Charles-de-Gaulle, France) (Polidocanol/Laureth 9). Further, Yamasuji et al [29] reported a case of concurrent, SPT-confirmed hypersensitivity to PEG 6000, polysorbate 80, hydroxyethylated starch and poloxamer, while Badiu et al. [39] recently identified a PEG-hypersensitive patient with positive SPT to polysorbate 80. A patient from our centre with confirmed allergy to PEG 6000 and 3000, was positive in SPT to polysorbate 80 performed after an anaphylactic reaction to polysorbate 80-containing chlorhexidine [26]. In vitro studies of cross-reactivity show a similar picture: development of a PEG antibody assay has necessitated the removal of polysorbate due to cross-reactivity with PEG APAb assays [1].

Unlike PEGs, immediate-type hypersensitivity to PEGylated drugs is well established. Reports of HSRs to PEGylated interferon (PEG-IFN) in cases where conventional interferon was tolerated have been described [54–57], inducing potentially protracted HSRs due to increased MW and circulation time of PEGylated drugs [58]. A case of clinical PEG hypersensitivity with positive SPTs to both PEG-IFN and PEG [23] introduces the possibility of cross-sensitization to PEGylated drugs in instances of PEG sensitization. Recently, a desensitization protocol for PEG-IFN was successfully devised [59]. Due to notable environmental PEG exposure and severity of immediate-type PEG hypersensitivity, a desensitization protocol for conventional PEG products would be desirable. However, no such protocols have been attempted and may require an individualized approach using the exact HSR-inducing PEG product(s).

Cross-reactivity between PEGs, PEGylated drugs and structurally similar PEG derivatives exists but is likely underestimated. In instances of hypersensitivity to PEG products or PEG derivatives therefore, cross-sensitivity should be investigated due to the severity of PEG-related HSRs and the likelihood of future exposure in household and healthcare settings.

Immunological mechanisms of immediate-type PEG hypersensitivity

Numerous immunological mechanisms have been suggested for immediate-type PEG hypersensitivity. It is likely that PEGs interact with the immune system in several ways, capable of inducing both specific and non-specific recognition. Indication of PEG's non-specific immunological interaction was obtained in the 1950s, when PEGs were shown to induce blood clotting and cell clumping [12]. More recently, complement activation in human serum by monodisperse, endotoxin-free PEGs has been demonstrated, likely occurring via the lectin and alternative complement pathways [60]. But although complement has been shown to play a role in HSRs to PEG-conjugate agents [12], scant evidence indicates complement activation to be the cause of HSRs to conventional PEG-containing products; in a single report by Hesselbach et al. [17], measurement of complement in a patient with immediate-type PEG hypersensitivity found values of C3 and C4 within the normal range. Furthermore, as complement is not preserved in the process of histamine release (HR) testing, a complement-mediated mechanism is unlikely in patients with positive HR test to PEGs.

The ability of the immune system to mount a PEG-specific response is established [1]. However, most studies focus on the antigenicity of PEG-conjugate agents with subsequent development of antibodies specific to PEG, rather than PEGs acting as complete antigens on their own. Accordingly, Meller et al. [57] detected T cells specific for PEG-IFN but not conventional interferon in a subset of patients with PEG-IFN-associated exanthemas and positive intradermal tests. Lesional skin of exanthemas further showed induction of TH2-associated chemokines. Richter and Akerblom [61] found PEG antibody responses (predominantly IgM and clinically insignificant) in 50% of patients undergoing subcutaneous immunotherapy with ragweed and honeybee venom extracts modified with methylcapped PEG after two weeks. The literature indicates a rising prevalence of PEG-specific IgM and IgG antibodies in patients treated with PEG-conjugated agents as well as in healthy subjects: while Richter et al. [61]demonstrated anti-PEG in 3.3% and 0.2% of an untreated atopic and healthy study population, respectively, in 1983, a 2012 study reported anti-PEG IgG and M in 20–25% of 350 healthy blood donors [62]. Myler [1] found pre-existing anti-PEG IgM and IgG in approximately 10% of patients naïve to PEG-conjugate treatment, although HSRs to PEGs were not reported in the same population. The apparent increase in PEG antibodies among both PEG-conjugate-treated and untreated populations could be due to improved detection techniques. However, the role of increased PEG exposure should be considered [1].

In the reviewed cases of PEG hypersensitivity, several authors interpret patient's clinical history and diagnostic findings to be indicative of an IgE-mediated PEG allergy [15, 20, 25, 27, 31, 39, 40, 43, 63]. Allergy testing with PEGs, including 86% of performed SPTs, all four conclusive IDTs and all four cases of oral provocation, elicited responses indicative of IgE-mediated allergy. Still, Hesselbach et al. [17] could not identify significant levels of PEG 8000-specific IgE in a patient allergic to PEG 8000 using RAST, and in vitro studies described by Hyry et al. [14] failed to confirm PEG 6000-specific IgE in patient serum as the non-atopic control demonstrated similar binding in immunospot. Significant technical challenges to the development of PEG assays exist due to the small repeating structure the polymer, the structural homology of PEG to detergents/derivatives (i.e. polysorbates) used in the process, the low affinity of PEG antibodies and the challenges of producing relevant positive controls [1]. To date, PEG-specific IgE has yet to be directly identified in a patient with clinical symptoms of PEG hypersensitivity. But while specific IgE has not yet been directly detected, basophil studies have offered some insight. In two separate PEG cases, BAT and basophil histamine release tests (HR test) showed positive basophil responses upon PEG challenge [15, 27], indicating a possible role of IgE. Still, basophil studies alone may only limit the immunological mechanism to an unidentified serum factor.

Finally, compelling evidence of an IgE-mediated mechanism was suggested in an inhibition study where abolishment of PEG 3350- and PEG 6000-induced histamine release was achieved via pre-incubation of a PEG-sensitized patient's blood with monomeric and dimeric fractions of PEG (ethylene glycol and diethylene glycol) [27]. Inhibition was antigen specific, as anti-IgE induced histamine release regardless of ethylene and diethylene pre-incubation of patient blood. These findings suggest that monovalent ethylene glycol and diethylene glycol specifically bind and occupy serum factors – potentially IgE – on patient basophils, thereby blocking later attachment of PEG. That monomeric and dimeric fractions do not induce histamine release on their own, may be due to the necessity of longer polymer chains to cross-bind antibody receptors. In the same study, further evidence of an IgE-mediated mechanism was provided when preincubation of the same patients' blood with Omalizumab (Novartis, Copenhagen, Denmark) (IgE-blocking antibodies) prior to passive HR tests, similarly abolished PEG-mediated histamine release [27]. Taken together, these results make an IgE-mediated mechanism behind some cases of PEG hypersensitivity plausible.

Allergy investigation

The extent of diagnostic testing varied greatly among reviewed cases. In 13 (35%) reports, the PEG hypersensitivity diagnosis was based on clinical history alone. Among the 22 (60%) patients who underwent SPT with PEGs, 19 (86%) developed positive reactions to at least one MW using test concentrations ranging from 0.0001% to 100%. Two of three remaining patients with negative SPT results – all for PEG 4000 at 0.1–100% concentration – developed positive reactions to intradermal tests (IDT) with PEG 4000 at 0.1% and 0.0001% as well as oral challenge [63]. The third patient with multiple HSRs to PEG 4000-containing products was negative in SPT (100%), IDT (0.1%) and patch testing for the polymer [43]. The explanation for this lack of response is unclear.

Systemic reactions including urticaria and cough were reported in two cases following SPT: the first involving testing with 1% solution of the high MW PEG 8000 [17] and the second in which multiple MWs (PEG 6000, 3000 and 300) were tested simultaneously and in duplicate [26]. Importantly, the study reported that SPT results for PEG 3000, 6000 and polysorbate 80 were slow to develop in comparison with positive controls. These findings imply that SPT with multiple and

particularly high MWs simultaneously should be conducted using a cautious stepwise approach. SPT in patients with a history of severe HSRs should be initiated using dilute PEG concentrations. Furthermore, interpretation of SPT results for PEG's should not be concluded before 30 min.

Intradermal test concentrations ranged from 0.0001% to 10% [20, 28, 43, 63]. Three of five (40%) IDTs resulted in systemic reactions with 10% PEG 3350 and 0.1% PEG 4000, inducing anaphylaxis in two instances [28, 63]. The relatively high risk of systemic responses indicates that IDTs should only be carried out using very dilute solutions in skin prick test-negative patients.

Oral challenge was conducted in three cases using PEG 4000, all of which were positive [31, 63]. Two cases of oral challenge provoked systemic symptoms that required immediate treatment [31, 63]. Due to the risk of severe reactions, oral challenge with PEGs should thus not be attempted for diagnostic purposes unless SPT and IDT are negative.

Although investigated in two cases, in vitro studies using RAST could not identify PEG-specific IgE. Methodology was in neither case described. Measurement of the monomer ethylene oxide-specific IgE was likewise negative in two studies [15, 39]. Basophil studies were described in four cases using PEG 400, 3350, 4000 and 6000. Two cases produced positive results: the first for PEG 3350 and 6000 using a previously described basophil HR method [27, 64], the second using the CD203 BAT with PEG 4000 and 6000 [15]. Both reports found correspondingly positive SPT results. The two other studies produced negative results in BAT for PEG 400, 3350, 4000 and 6000, despite positive SPT and IDTs for the same MWs [28, 39]. It is possible that these patients could be characterized as non-responders in basophil studies [65].

Of cases where patch testing was performed following immediate-type HSRs, results were invariably negative [8, 15, 41, 63]. In two such cases however, open test by rubbing the offending PEG-containing product on the patients arms provoked an urticarial response [41, 42]. Incidentally, concurrent immediate- and delayed-type PEG hypersensitivity has yet to be described; among 15 instances of reported delayed-type PEG hypersensitivity, none investigate for simultaneous immediate-type hypersensitivity. Of note, all delayed-type cases involve application of PEG on broken skin, often in combination with known sensitizers such as nitrofurazone [42, 66–68]. In contrast to immediate-type hypersensitivity, low molecular weight PEGs were more commonly associated with delayed-type HSRs, likely a reflection of their comparatively greater cutaneous absorption and prevalence in topical products [69, 70].

In sum, standardized diagnostic management of patients suspected of hypersensitivity to PEG is lacking from the literature. Since October 2012, the Danish Anaesthesia Allergy Centre (DAAC) has routinely tested patients with unresolved drug allergy using a standardized PEG SPT panel that includes maximum concentrations of PEG 300 (100%), 3000 (10%) and 6000 (50%). Insufficient experience has been gathered to suggest ideal skin test concentrations and careful titration starting

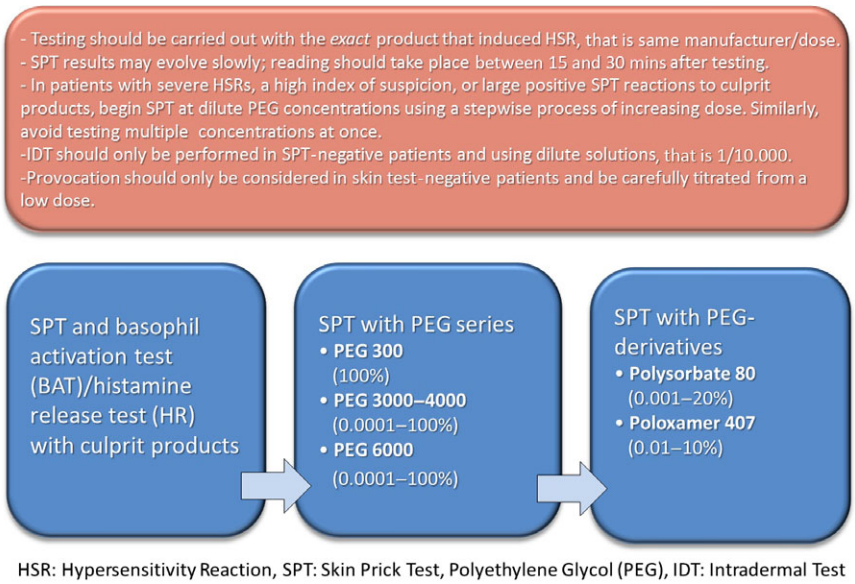

Fig. 3. Proposed algorithm for allergy investigation of patients with suspected immediate-type polyethylene glycol (PEG) hypersensitivity. The algorithm is based on the literature review; in addition, authors experience investigating six PEG-hypersensitive patients. The algorithm includes a range of PEG and PEG-derivative test dilutions (%) reported to have showed positive response in skin prick test (SPT).

with dilute solutions may be indicated in patients with very severe reactions. However, based on allergological investigations presented in this literature review, as well as experience gained from six PEG-hypersensitive patients and >150 healthy negative controls tested at our centre, we suggest an algorithm for allergy investigation of suspected immediate-type PEG hypersensitivity and include a range of PEG concentrations reported to have showed positive response in SPT (Fig. 3).

In conclusion, PEGs can in rare cases cause immediate-type HSRs, ranging in severity from urticaria to life-threatening anaphylactic shock. Perioperative, medical and household products as diverse as tablets, bowel preparations, ultrasound gels, shampoos and oral hygiene articles have been linked to PEG HSRs. As excipients, PEGs rarely raise suspicion and commonly figure as 'hidden allergens'. A lack of both standardized ingredient labelling and sufficient brand name documentation on medical charts further complicates the implication and avoidance of PEGs. A shared feature of many cases of PEG hypersensitivity is thus a history of repeated severe HSRs to seemingly unrelated products, different brand names of the same drug, different doses of the same brand name and incorrect labelling as idiopathic allergy.

The need for increased awareness of PEG's sensitizing potential is clear. Cases of cross-sensitization between PEGs of various MW, PEGylated drugs as well as PEG derivatives, further underline this need. This review illustrates not only the prevalence of PEG, but describes the often severe clinical picture of PEG-HSRs. We emphasize the importance of testing with *exact* culprit products as well as individual constituents – including excipients. Furthermore, we caution that products typically thought to be innocuous, including lubricants, ultrasound gels, anaesthetic sprays and bandages, not be above suspicion during allergological investigation. To aid allergists in the management of these rare patients, we present recommendations for instances where PEG hypersensitivity should be considered and present a diagnostic algorithm (Table 3, Fig. 3).

At present, the scope of PEG hypersensitivity remains unknown but is likely underreported. With the mounting prevalence of PEGs and structurally related compounds in medical and household products, as well as in drug-delivery technology, a rise in incidence of PEG hypersensitivity may be expected. Accordingly, allergists must be mindful of this rare, but important diagnosis.

Conflict of interest

Neither E. Wenande nor LH. Garvey have any conflicts of interest to disclose.

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