

Polyethylene Glycols (PEG) and Related Structures: Overlooked Allergens in the Perioperative Setting

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We describe hypersensitivity to polyethylene glycols (PEGs), with cross-reactivity to a structural analog, polysorbate 80, in a 69-year-old patient with perioperative anaphylaxis and subsequent, severe anaphylactic reactions to unrelated medical products. PEGs and PEG analogs are prevalent in the perioperative setting, contained in a wide range of products seldom suspected of causing hypersensitivity reactions and thus rarely documented in surgical/anesthetic records. We suggest routine testing for PEGs after perioperative anaphylaxis because exposure to these polymers often is significant. Comprehensive brand name documentation on the anesthetic chart of all product exposures is central to identifying the responsible allergen. (A&A Case Reports. 2015;4:61–4.)

Polyethylene glycols (PEGs) or macrogols are hydrophilic polymers of varying molecular weight, ranging from 200 to 50,000 g/mol. In the pharmaceutical nomenclature, the rounded average molecular weight (g/mol) of PEG chains in a given product is denoted by a number, for example, PEG 4000. Best known as the active agents of common bowel evacuants, the widespread use of PEGs as solvents, surfactants, lubricants, dispersants, and drug-delivery vehicles (PEGylation) is less recognized. Although generally considered biologically inert, severe hypersensitivity reactions to PEGs have been described with increasing frequency along with their expanding use.^{1–5} In the perioperative setting, PEGs are included in a wide range of products seldom suspected of causing anaphylaxis and thus rarely noted in surgical/anesthetic records (Fig. 1). This lack of documentation, combined with insufficient and nonstandardized labeling, likely leads to underreporting of PEG hypersensitivity in the perioperative setting.

In this article, we describe a patient with perioperative anaphylaxis and subsequent, severe anaphylactic reactions to unrelated products. We identified the cause to be hypersensitivity to PEGs with cross-reactivity to a structural analog, polysorbate 80.

Written consent to submit this case report for publication was obtained from the patient.

CASE DESCRIPTION

A 69-year-old man underwent emergency surgery for an acute subdural hematoma with impending cerebral herniation. General anesthesia was induced with thiopental, alfentanil, and cisatracurium and maintained with remifentanyl and propofol. Routine antibiotic prophylaxis with

cefuroxim IV was administered. After induction, his arterial blood pressure was labile despite infusion of 1000 mL of normal saline and repeated bolus doses of ephedrine and phenylephrine. Infusion of norepinephrine was started, and his mean arterial blood pressure (MAP) stabilized at 85 mm Hg. Twenty minutes later, an hour into the procedure, he developed sudden onset hypotension (MAP 35 mm Hg and heart rate 100 bpm) and generalized urticaria. Anaphylaxis was suspected, and the norepinephrine infusion was increased with no effect. His blood pressure stabilized after repeated bolus doses of 0.05 mg epinephrine. Propofol and remifentanyl infusions were stopped and anesthesia was switched to sevoflurane. IV steroids and antihistamines were administered and the surgical procedure was completed. Serum tryptase was not increased at 4.97 µg/L 1 hour after the reaction. Baseline serum tryptase was 4.27 µg/L.

After surgery, the patient's trachea remained intubated, and he was sedated with propofol and remifentanyl. After transfer to intensive care, an epinephrine infusion was necessary to maintain MAP >75 mm Hg. After stabilizing during the subsequent 8 hours, the patient was extubated uneventfully. On the third postoperative day, he developed a new urticarial rash affecting his hands, knees, and feet, while vital variables remained stable. The preceding antibiotic treatment and blood transfusions were suspected as causative agents. The patient recovered during the next 5 weeks and was then discharged home. During this period, he complained of recurrent itching localized to his face and trunk. No cause was identified, and he received daily antihistamine treatment with 10 mg cetirizine.

Four months later and a few minutes after taking the first tablet of Deprakine® Retard (valproate), a new formulation of his daily antiepileptic medication, he recalled feeling intense generalized itching before becoming unresponsive. When the paramedics arrived, they noted widespread urticaria and hypotension (MAP 49 mm Hg and heart rate 100 bpm). He was treated with 0.3 mg epinephrine IM, steroids, antihistamines, and fluids. The antiepileptic treatment was switched to levetiracetam with no further reaction.

Two months later, he again experienced generalized flushing, itching, dizziness, and hypotension. The only exposure was Grepid®, a new formulation of clopidogrel, and levetiracetam 6 to 8 hours earlier. Because of the initial

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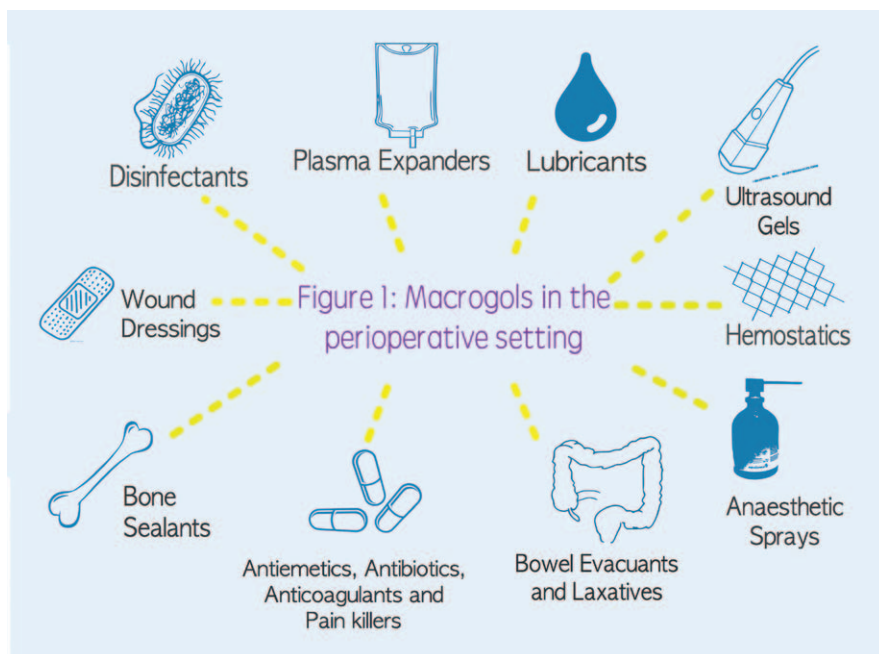


Figure 1. Prevalence of polyethylene glycols or macrogols in the perioperative setting.

perioperative reaction, he was subsequently referred to the Danish Anaesthesia Allergy Centre, where he underwent investigations with a combination of skin prick tests (SPTs), intradermal tests, specific immunoglobulin E (IgE), histamine release, and provocation with all documented drugs and products he was exposed to before the perioperative reaction, including latex and hidden allergens: chlorhexidine, ethylene oxide, methylcelluloses, and PEGs.

PEGs were tested using SPT alone as intradermal tests and provocation have been linked to systemic reactions.³⁻⁵ SPTs were positive for PEG 6000 and PEG 3000 in our patient. SPT for PEG 300 as well as tests for all other drugs he had been exposed to perioperatively were negative. Despite vigorous checks of all perioperative documentation, no specific PEG-containing product could be identified. Through contact with the involved neurosurgical and anesthetic departments however, we identified PEG-containing products thought to be the possible undocumented exposures: chlorhexidine disinfectant, xylocaine spray, lubricating gel for tracheal intubation and bladder catheterization, and the dural sealant (DuraSeal®; Covidien). In the intensive care unit, the patient had documented exposure to PEG-containing Toilax® (bisacodyl). PEG 3000, PEG 3500, and PEG 6000 were identified in Deprazine Retard (valproate) and Grepid (clopidogrel), the 2 drugs implicated in the patient's subsequent reactions. As a consequence, he was warned against further exposure to PEGs/macrogols.

Eighteen months after the initial anaphylactic episode, the patient was diagnosed with esophageal cancer. Close cooperation between the local and regional pharmacy and doctors at the Danish Anaesthesia Allergy Centre was established to ensure that planned treatment was PEG-free. He underwent insertion of a peripherally inserted central catheter for IV access. During the procedure, colored chlorhexidine 0.5% containing polysorbate 80 was applied generously to the puncture site. Polysorbate 80 is derived from PEGylated sorbitan.

Similar to PEGs, polysorbates exhibit the chemical moieties: $-(\text{CH}_2\text{CH}_2\text{O})_n$ and $-\text{OCH}_2\text{CH}_2\text{OH}$. Within minutes of the line being inserted, the generalized flushing was noted and the patient felt faint and became hypotensive (MAP 47 mm Hg and heart rate 110 bpm). Hemodynamic stability was achieved by raising his legs and administering IV antihistamines, fluids, and steroids. His serum tryptase was 11.2 $\mu\text{g/L}$ 1 hour after the reaction. Baseline serum tryptase was 5.85 $\mu\text{g/L}$.

Some weeks later, radiation treatment resulted in superficial burns on the patient's chest. A Mepilex® bandage was applied to the damaged skin. Over the next hour, he experienced sneezing and localized erythema followed by generalized itching and urticaria. The bandage was removed and symptoms remitted. PEGs were later identified as "hidden" components of the Mepilex® bandage.

SPT with colored chlorhexidine 0.5% (containing polysorbate 80), plain polysorbate 80 (200 mg/mL = 20% w/v in water), and inner and outer surfaces of the Mepilex bandage were all positive after 20 minutes. SPT with chlorhexidine not containing polysorbate 80 was negative. All above tests were negative in 2 controls.

DISCUSSION

PEGs of high molecular weight (>1000 g/mol) with cross-reactivity to the structural analog polysorbate 80 were concluded to have caused the severe hypersensitivity reactions in the patient. This is the second case reported of anaphylaxis after perioperative PEG exposure.¹ Upon avoidance of PEG and polysorbate 80, the patient has had no further episodes during a follow-up of 8 months. An IgE-mediated mechanism for PEG hypersensitivity has previously been demonstrated,² and in this case, clinical presentation and positive SPT results point to a similar mechanism. Unfortunately, a validated PEG-specific IgE measurement has yet to become available.

The mode of PEG antigenicity is likely multifaceted. Investigations of the haptogenic qualities of PEGs reveal

Table 1. PEGs and PEG-Analog-Containing Products Common to the Perioperative Setting

Product group	Product examples ^a (table not exhaustive)
Bowel evacuants/laxatives	Movicol [®] , Moviprep [®] , Moxalole [®] , SoftLax [®] , MiraLax [®] , ClearLax [®] , DulcoLax [®] , GlycoLax [®] , Bohm [®] Evacuant, Golytely [®] , Fortrans [®] , Kleanprep [®] , Cologep [®] , Casenlax [®] , Lacrofarm [®] , Magenterol [®] , Toilax [®] (bisacodyl)
Disinfectant sprays/gels	Chlorhexidine solution, Povidone Iodine Gel-Cream
Local anesthetics	Xylocain [®] Spray (lidocaine), Hurracaine [®] Topical (benzocaine), Americaine [®] Topical (benzocaine), Lidocaine ointment USP, Gelato [®] Topical (benzocaine)
Ultrasound/lubricant gels	Naqi [®] Ultrasound gel, Sonigel [®] Ultrasound Lotion
Hydrogels as hemostatic agents and tissue sealants	Dura Seal [®] , AdvaSeal-S [®] , Focal Seal [®] , CoSeal [®] , ReSure [®] Sealant, Nobagel [®] , Biolex [®] Wound Gel, Carrasyn [®] Fel Wound, Elasto-Gel [®] , Instra-site Gel [®] , Skin-Tegritty [®] Hydrogel, Tender Wet [®]
Plasma expanders	PEG-Alb, PEG-HSA, Hespan [®] , Hestar [®] , Voluven [®]
Absorbable wound dressings	Curapor [®] , Mepilex [®] , Epimax [®] , Vigilon [®] , N-Terface [®] , Conformant 2 [®] , Inadine [®]
Pain relief/anti-inflammatory drugs	Panodil [®] (paracetamol), Pinex [®] (paracetamol), Spifen [®] (ibuprofen), Burana [®] (ibuprofen), Contalgin [®] (morphine), Tradolan [®] (tramadol), Ketogan [®] (dimethylaminodiphenylbuten & ketobemidone), Reltebon [®] Depot (oxycodone), Jurnista [®] (hydromorphone)
Antibiotic, antiemetic, anticoagulant, and antacid drugs	Domperidone [®] Actavis, Ondansetron [®] Actavis, Pantoprazol Nycomed [®] , V-Pen Mega [®] (V-penicillin), Grepid [®] (clopidogrel), Xarelto [®] (rivaroxaban), Balancid Novum [®] (calciumcarbonat, magnesiumhydroxid), Magnesium Medic [®]

PEGs = polyethylene glycols.

^aNot all preparations and doses of the same generic drug contain PEGs or PEG analogs.

that exposure to PEG-conjugated drugs can elicit an anti-PEG response⁶ in which PEGs possibly act as incomplete antigens. However, with increasing molecular weight, unconjugated PEGs are likely to act as complete antigens because of their size (200–50,000 g/mol) and chain length. In this case, we suspect high-molecular-weight PEGs to act as complete antigens.

Normal baseline values for serum tryptase suggested by the manufacturer are <11.4 µg/L. Tryptase values are very reproducible in the perioperative setting,⁷ leading to suggestions that a clinically relevant increase in serum tryptase also can be seen within the normal range.^{7–9} Tryptase sampled at the time of reaction should therefore always be compared with a baseline sample taken >24 hours later⁷ and levels <11.4 µg/L that show an increase of >2 µg/L or 135% above baseline remain suggestive of anaphylaxis.^{8,9} After the polysorbate 80-induced anaphylaxis, the tryptase levels of the patient were significantly increased (11.2 µg/L) in comparison with his baseline value (5.85 µg/L). In contrast, tryptase measured 1 hour after the perioperative reaction (4.97 µg/L) showed no significant difference from baseline (4.27 µg/L). The cause of this discrepancy is uncertain but may partly be attributed to dilution by fluids administered in the perioperative setting.⁷ Furthermore, studies have shown that tryptase is not always increased in cases of clinical anaphylaxis.¹⁰

Reports of hypersensitivity to PEGs and polysorbates appear separately in the literature.^{1–5,11,12} To our knowledge, cross-reactivity between these 2 polymers has only been described once before.¹ Because of the shared chemical moieties of $-(\text{CH}_2\text{CH}_2\text{O})_n-$ and $-\text{OCH}_2\text{CH}_2\text{OH}$ —in both PEG and polysorbate, however, the potential for cross-reactivity remains possible. Therefore, in patients with confirmed PEG hypersensitivity, testing for cross-reactivity with polysorbate 80 should be considered.

PEGs, PEG analogs, and other related polymers are prevalent in hospital and perioperative settings (Table 1). Recently, the potential for hypersensitivity reactions to not only active ingredients but also additives such as PEGs, polysorbates, and even methylcelluloses¹³ has been reported. Increased awareness of these and potentially

other hidden allergens in the perioperative setting is important.¹⁴ The rarity of perioperative anaphylaxis and the many potential exposures are challenges to correct identification of culprit products. We suggest including SPT for PEGs when investigating perioperative anaphylaxis because exposure to these polymers is often significant. Also, comprehensive documentation on the anesthetic chart of brand names of all exposures, including those not normally thought to have allergenic potential, is crucial to identifying the responsible allergen. ■■

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Editorial Comment: Ultrasound-Guided Peripheral Nerve Blocks for Ventricular Shunt Revision in Children: Erratum

In the article, “Editorial Comment: Ultrasound-Guided Peripheral Nerve Blocks for Ventricular Shunt Revision in Children,”¹ that appeared on page 160 in the December 15, 2014 issue of *A&A Case Reports*, the first sentence is incorrect. The sentence states “...postoperative pain management of 22 pediatric patients...” The sentence should say “... post-operative pain management of 2 pediatric patients....”

Reference

1. Mariano ER. Editorial comment: ultrasound-guided peripheral nerve blocks for ventricular shunt revision in children. *A&A Case Reports* 2014;3:160–1

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