Polyethylene-glycol: the neglected culprit of hypersensitivity reactions



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Introduction

Polyethylene glycol (PEG), which is also known as macrogol, is widely used as an excipient in pharmaceutical products and other products such as processed food and cosmetics. They have a broad spectrum of usage in both medical and commercial settings, with molecular weights (MW) that range from 200 to 20,000 grams/mol.[1]

PEGs were generally considered to have low toxicity and to be biologically inert, features which have contributed to their widespread use. They are usually found as the active ingredient in laxatives and bowel preparations, and they are also used as pill binders and stabilizer in depot injections or liquids for injection.[2] PEGylated drugs can prolong the circulation time of systemic drugs by impeding metabolism or shielding the drug from immune-degradation, and therefore they are becoming more common in drugs.[2] However, there have been an increasing number of case reports regarding immediate-type allergy to PEGs recently in the literature.[2-4]

Clinical presentation of PEG anaphylaxis

The onset of hypersensitivity reactions and anaphylaxis to PEG is typically rapid and severe. Common symptoms include pruritus, urticaria, flushing and angioedema. Hypotension or airway symptoms, including chest tightness and dyspnea, occurs in severe cases.[5]

Mechanism of anaphylaxis

The mechanism(s) that cause(s) PEG allergy are still unclear. IgE antibodies against PEG have been detected in some patients with a history of PEG-induced anaphylaxis.[6] Some research have also demonstrated the ability of PEGs to induce complement activation, at least in vitro, and may result in complement activation-related pseudo-allergy (CARPA).[7] However, human data relating to complement activation as a mechanism responsible for acute allergic reactions to PEG remain inconclusive.[5]

Back in 1984, Richter and Akerblom first demonstrated that half of patients treated with monomethoxy polyethylene glycol modified ragweed extract and honeybee venom could develop an anti-PEG antibody (predominantly of the IgM isotype) reaction, but the study considered the IgM responses to be weak and the ouctomes have no major clinical significance. Also, naturally occurring PEG antibodies were present in 0.2% of healthy blood donors.[8] Nonetheless, 20 years later, Armstrong et al reported a much higher incidence rate of anti-PEG antibodies (27%-28%), mainly IgG, among normal healthy subjects. More recently, the incidence rate was found to be even higher (approximately 42%).[9] These data suggest that there has been an exponential exposure over time to these substances among the general population because there are gaining popularity of PEGs in daily consumer products, such as pharmaceuticals, cosmetics, processed foods and in industrial manufacturing.[10] This growing widespread exposure to PEG-containing products likely led to the formation of more anti-PEG antibodies in the general population. Consequently, the introduction of PEGylated drugs has increased the attention of clinicians, researchers and government officials toward the true immunogenic and allergenic potential of these polymers, that the pre-existent PEG antibodies may induce serious hypersensitivity reactions in patients treated with PEGylated drugs.[10-11]

Management of PEG allergy

Handling patients with PEG hypersensitivity can be challenging because of the extensive allergologic workup required and the limited avoidance options as many drugs, including those used for the treatment of allergic reactions such as antihistamines, may contain PEG as an additive.[12-13] Unfortunately, comprehensive avoidance lists are difficult compile, as medical preparations frequently change; thus, awareness is key. Specific product labelling and a high level of awareness are crucial. Patients are advised to discuss with doctors or pharmacists should they have any concerns about potential allergic reactions.

Apart from oral medications, PEG or macrogol are also commonly found in vaccines as one of the excipients. Necessary precautions must be taken when prescribing vaccines for patients to avoid potential hypersensitivity reactions. A summary of the vaccine excipients are included in Table 1, in view of current COVID-19 pandemic.

Conclusion

There have been increasing numbers of PEG hypersensitivity cases across the world. The precise mechanism(s) for such reactions remains unclear. IgE antibodies and complement activation may be potential underlying reasons, but further research is

needed for us to have a better understanding about this phenomenon. Caution must be taken when prescribing medications or vaccines since PEG are commonly used as excipients in these products. Patients are advised to consult doctors and pharmacists should they have any enquiries regarding the excipients of medical products.

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Table 1. Vaccines against SARS-Cov-2 planned to be available in Hong Kong (at the time of this writing: 27 February 2021)[14-18]

Vaccine & Manufacturer	Vaccine Type	Excipients	Hypersensitivity data up to date
CoronaVac (Sinovac, China)	Inactivated vaccine (formalin with alum adjuvant)	Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride	No anaphylaxis events reported during Phase 3 trials (33,620 participants) Incidence of hypersensitivity following immunization was about 6.2 per 100 000 participants. Among the participants with allergic reactions, one third of them have baseline history of allergic diseases
BNT162b2 (Pfizer-BioNTech)	mRNA-based vaccine (encoding the viral spike (S) glycoprotein)	(4-hydroxybutyl) azanediyl)bis (hexane6,1-diyl)bis(2- hexyldecanoate)] (ALC0315), **2- [(polyethylene glycol)-2000]**-N,N-ditetradecylacetamide (ALC-0159), 1,2-distearoyl-snglycero-3-phosphocholine cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, water for injection	No anaphylaxis events attributed to vaccine reported in clinical trials (~22,000 participants randomized to active dosing) Post-marketing experience in UK, Canada and US showed two cases of reactions out of 138 000 persons vaccinated. According to the Morbidity and Mortality Weekly Report issued by US Centres for Disease Control and Prevention, during the period of 14 to 23 December 2020, 21 cases of anaphylaxis after administration of a reported 1 893 360 first doses of BNT162b2 (11.1 cases per million doses) were detected
AZD1222* (Oxford/AstraZeneca)	Replication deficient viral vector vaccine (adenovirus from chimpanzees)	L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, **polysorbate 80,** ethanol, sucrose, sodium chloride, disodium edetate dihydrate, water for injection	No anaphylaxis events reported in clinical trials (~12,000 participants randomized to active dosing) No cases of AZD1222-related anaphylaxis was reported so far

*AZD1222 will not be available in 2021, according to government announcement.