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Polyethylene glycols and polysorbates: Two still neglected ingredients causing true IgE-mediated reactions

We have read with great interest the article by Stone et al[1] because it is a strong alert to physicians to focus their attention toward the increasing role of drug excipients in the genesis of immediate-type reactions, which can be genuinely IgE mediated too. Furthermore, the authors demonstrated that even polysorbates may be responsible for IgE-mediated reactions because of their cross-reactivity with the polyethylene glycols (PEGs) caused by common chemical epitope, whereas it had been previously suggested that polysorbates caused nonimmunologic hypersensitivity.[2] PEGs or macrogols are linear or branched polymers with repeating ethylene oxide subunits and different molecular weights, ranging from 200 g/mol up to 10,000 g/mol according to the length of their chains.[3] Recently, a high prevalence of pre-existing anti-PEG IgM and IgG antibodies have been detected in the plasma of healthy donors.[3]

In 1984, Richter and Akerblom[4] first demonstrated that 50% of allergic patients treated with monomethoxy polyethylene glycol modified ragweed extract and honeybee venom could develop an anti-PEG antibody predominantly of the IgM isotype, but they considered that weak IgM responses having no clinical significance and naturally occurring PEG antibodies were present in 0.2% of healthy blood donors. However, 20 years later, Armstrong et al[5] reported a much higher incidence rate of anti-PEG antibodies (27%-28%) among normal healthy subjects, mainly IgG, whereas more recently the incidence was found to be even higher (approximately 42%).[3] Beyond the improvement of laboratory techniques to isolate and dose anti-PEG antibodies, these data suggest that there has been an exponential exposure over time to these substances among the general population because PEGs are widely used in daily consumer products as cosmetics, processed foods, pharmaceuticals, and in agricultural or industrial manufacturing.[3] PEG-containing surfactants, as well as PEG itself, can be found in many household and hygiene products (eg, soap, shampoo, toothpaste, lotion, detergent).[6] For that reason, it is natural to assume that nowadays such widespread exposure to PEG-containing products has led to the inevitable formation of anti-PEG antibodies in the general population. Subsequently, the introduction of PEGylated drugs has increased the attention of physicians and researchers toward the true immunogenic and allergenic potential of these polymers,[3,7] showing that pre-existent PEG antibodies may induce serious hypersensitivity reactions in patients treated with PEGylated drugs.[8]

Despite the increased studies on PEG molecules,[3,7] the mechanisms leading to PEG hypersensitivity are poorly understood, although Yang and Lai[3] speculated that injured skin or mucosa results in local inflammatory responses with recruitment of immune cells. When local inflammation is treated with cleaning substances that contain PEGs as soaps, detergents, and disinfectants, a secondary immune response may develop toward these polymers. The persistent exposure due to the ubiquitous presence of PEGs in the environment induces recruitment and activation of immune memory mechanisms.[3] However, the identification of patients affected by PEG sensitization is still a challenge, because no clear risk factors for developing PEG or polysorbate hypersensitivity have been identified. So, the diagnosis of PEG/polysorbate hypersensitivity can be particularly arduous, requiring an extensive allergic workup with skin tests for PEG molecules with different molecular weights and PEG-containing drugs, which often elicited the immediate-type reaction. The same procedure needs to be performed with challenge tests while *in vitro* IgE tests are still experimental.[1] From a general review of the literature, we have proposed, on the basis of a pragmatic approach to the problem, that PEG hypersensitivity is most likely to develop in patients during 2 well-identified situations[9]:

- following ingestion of PEG as preparation for a colonoscopy examination, due to PEGs' laxative effect bound to their hyperosmolar properties;
- following administration of PEGylated therapeutic agents;

while it should be strongly suspected:

- following cutaneous application of topical drugs or cosmetics with the onset of a contact urticaria/anaphylaxis, as confirmed by other case reports[9,10];
- following the ingestion or administration of different chemically unrelated medications containing PEGs as excipients, including corticosteroid formulations.[9]

Yet, there is the problem of cross-reactivity, not only between PEG and polysorbate, but even among the various PEG molecules of different molecular weights and lengths, that is, another issue that has been scarcely investigated,[9] because it has been presumed that cross-sensitivity occurs among PEGs of similar molecular weights.[9] In the light of increased exposure of PEGs and polysorbates in our environment, a greater incidence of PEG hypersensitivity should be expected in the next years. For that reason, we greatly appreciate the study of Stone et al because, along with the recent review of Garvey et al,[11] these reports point to the potential for hypersensitivity reactions to compounds that were reputed to be immunologically inert until a few years ago.

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