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Towards the best approach to PEG allergy

To the Editor,

We read with great interest the letter by Sellaturay et al.

It must be recalled that cross-reactivity between PEG and PEG derivatives including polysorbate, and among PEG derivatives, though rarely reported in clinical practice, does not have to be limited to skin tests. In 2015, Wenande et al.¹ described a case of anaphylaxis after perioperative exposure to polysorbate in a patient with previous anaphylactic reactions to PEGs; meanwhile, Kang et al.² followed the case of a patient who reacted to polysorbate and polyethoxylated castor oils, quite similar to the one reported by Bibera et al.³ Again, Wenande with Garvey in their subsequent brilliant review⁴ collected reports about individuals reacting to both PEG and other PEG derivatives, such as polyethylene glycol stearate,^{5,6} cetomacrogol⁶⁻⁸ and even to hydroxyethyl starch⁹; the following years' literature told us of clinically relevant reactivity to both PEG and polyoxyethylated castor oils¹⁰ and to both PEG and polidocanol.¹¹

Since PEGs are obtained from polymerization of ethylene oxide, their chemical structure has to be considered practically identical with the only difference of the chain length, which influences both skin test reactivity and clinical reactivity probably by increasing the likelihood of IgE capping as the chain length enlarges.^{12,13} Polysorbates are made up of four short PEG chains linked to a single sorbitan molecule; one of the PEG chains ends with an esterified fatty acid tail. Then, from an immunologic point of view, it seems possible to postulate that PEGs show a single epitope recognizable by IgEs (in a higher number of units, as the molecular weight increases), while polysorbates carry three possible epitopes – one of which is fully shared with PEGs. Then, cross-reactivity in immediate reading skin tests and immediate-type reactions to both PEGs and polysorbates (and, by extension, to any PEG derivative) would be easily explained, so that we could generally talk about a "PEG-epitope" that could expose PEG-allergic subjects to a high risk of reactions to PEG derivatives too. Upon this chemical basis, being the molecular weight of polysorbates (around 1300) quite close to that of PEG molecules contained in mRNA vaccines (2000), it is arguable that individuals who tolerated polysorbate-containing injected preparations without history of following reactions attributable to PEG allergy/pseudoallergy are more likely to receive both polysorbate- and PEG-containing vaccines uneventfully.

We do agree on the extreme caution to observe while performing skin tests with PEG epitope carrying products, especially in people who withstood severe reactions; but we also encourage intradermal testing when SPTs give negative results. As already proposed,⁴ end-point IDT concentrations (about 10 mg/ml for PEGs with MW 3,350–4,000^{14,15} and about 0.04 mg/ml for polysorbate

80 are not irritating¹⁵⁻¹⁷) must be reached gradually – and the same prudence has to be applied also to SPTs (end-point 60–250 mg/ml for PEG 4,000–6,000–20,000 and 0.4 mg/ml for polysorbate 80^{10,18-20}) – testing one product a time and keeping in mind that there are reports of slightly delayed cutaneous reactions with systemic symptoms (anaphylaxis).¹³ A final safety recommendation could be to observe for at least two hours those with a personal history of severe reactions to PEG or PEG derivatives when testing very high molecular weight PEGs.^{13,21} In fact, to date, skin tests (SPTs and – if needed – IDTs) represent the best way to confirm the suspicion of this kind of allergy, for they seem to have both very high sensitivity and specificity,^{3,12,22} thus usually allowing the avoidance of even more risky DPTs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Francesco Marchi made an extensive literature review and wrote the manuscript; Donatella Sutera and Anna Carabelli reviewed the manuscript.

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