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Editorial

Polyethylene glycol allergy . . . for real this time!

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Allergy to polyethylene glycol (PEG) is something most allergists had probably heard of, but seldom thought much about, until it was implicated as a possible cause of reactions to COVID-19 vaccines.[1] Although it turns out that PEG is not responsible for vaccine reactions,[2] renewed interest in PEG as an allergen has led to additional studies. A report in this month's issue of *Annals* describes the examination of a group of patients with PEG allergy, providing important new insights.[3]

PEGs are not proteins but rather polymers of ethylene oxide.[4] Their molecular weights range from 200 to 35,000, largely dependent on the number of repeating ethylene oxide units. As with all antibodies, IgE is almost always directed against protein, and thus, PEG would not be predicted to be allergenic. However, as with other nonprotein allergens, PEGs may act as haptens when bound to endogenous proteins, and the larger molecular weight PEGs may be allergenic themselves.

The study by Kayode et al[3] describes 42 patients seen in 4 large United Kingdom hospital systems over a 7-year period, who were determined to have IgE-mediated PEG allergy. Although this is one of the largest groups of such patients reported, the relatively small number from such a large patient population over an extended period implies that this is a rare allergy.

The patients ranged in age from 18 to 72 years. There was a female predominance, which has been seen in other studies and is theorized to be due to sensitization through PEG-containing cosmetics. As has been previously reported, the reactions tended to be quite severe, with 57% having anaphylactic reactions involving hypoxia, hypotension, or neurologic compromise and an additional 40% involving other respiratory, cardiovascular, or gastrointestinal symptoms. One of the reported clues to possible PEG allergy is a history of reactions to numerous unrelated medications that happen to contain PEG; however, although 2 patients reacted to 4 medications, 4 patients to 3, and 12 patients to 2; most (26) reacted only to a single medication.

Additional important observations from the study are that a small number of medications accounted for most reactions and that these medications contain relatively large amounts of higher molecular weight PEGs. The most implicated medications (29%) were intramuscularly administered depo preparations of methylprednisolone and medroxyprogesterone containing 29 mg and 20.3 mg of PEG 3350, respectively. The next most implicated medications (23%) were orally administered laxatives containing as much as 100,000 mg of PEG 3350. Systemic absorption of orally administered PEG may be less than 2%, but this would still be approximately 2000 mg. An additional 10% reacted to orally administered penicillin V tablets containing 6 mg of PEG 6000. Many of the patients who reacted to these medications tolerated other orally administered medications containing as much as 2.1 mg of PEG 4000, suggesting that there is a threshold below which reactions will not occur even in patients with PEG allergy. The concept of a threshold is further reinforced by 5 patients tolerating messenger RNA COVID-19 vaccines containing 0.05 mg of PEG 2000. In fact, hundreds of patients with known or suspected PEG allergy have received these vaccines uneventfully.[5,6]

There are no commercially available skin test reagents for PEG; however, this study provided guidance on appropriate testing using available materials. Skin prick tests were performed with PEG 3350, which is available in pure form as an over-the-counter laxative. Concentrations as high as 10% were used for skin prick testing and as high as 1% for intradermal testing; 51% of patients had positive skin prick test results, and an additional 34% had positive intradermal skin test results. The remainder had positive results when tested with higher molecular weight PEGs, suggesting that in addition to a quantity (milligram) threshold, there is also likely a molecular weight threshold. A few patients had mild systemic reactions to their intradermal skin testing. It is possible that had skin prick testing been performed with a higher concentration of PEG 3350, more patients would have had positive results, obviating the need for intradermal testing.

We seem to have gotten out over our skis in suggesting that reactions to messenger RNA COVID-19 vaccines were the result of PEG allergy, as it appears that the amount of PEG in the vaccines is not enough to provoke a reaction even in patients with PEG allergy. However, renewed interest in PEG as an allergen has allowed us to more thoughtfully identify and examine patients who may have this allergy, with the following lessons learned:

- PEG allergy is rare.
- Reactions to PEG can occur both to oral and parenteral administration.
- Reactions are more likely with larger amounts and higher molecular weights.
- There are likely thresholds in terms of both amount and molecular weight below which patients with PEG allergy will not react.
- Skin prick testing with more concentrated solutions of the readily available PEG 3350 will identify most patients.
- In patients with negative skin prick test results, intradermal skin testing with more dilute solutions will identify most of the remainder and may rarely cause systemic reactions.

Disclosures

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