

## Successful COVID-19 Vaccination of a Patient With Hypersensitivity to Polyethylene Glycol and Polysorbate

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J Invest Allergol Clin Immunol 2022; Vol. 32(4): 322-323  
doi: 10.18176/jiaci.0801

Key words: COVID-19. Skin testing. Allergy. PEG. Vaccination.

Palabras clave: COVID-19. Pruebas cutáneas. Alergia. PEG. Vacuna.

Soon after the mRNA vaccines Comirnaty (BioNTech/Pfizer) and Spikevax (Moderna) were approved for vaccination against COVID-19 infection, several cases of associated anaphylaxis were reported, with the excipient polyethylene glycol (PEG) suspected as elicitor [1-4]. Subsequently, administration of COVID-19 vaccines containing PEG or cross-reactive polysorbate was cautioned against in people with known hypersensitivity to PEG. We report the case of a 59-year-old woman who experienced anaphylactic reactions to PEG-containing drugs. The results of skin tests with PEG,

polysorbate, and COVID-19 vaccines were positive, as were those of the basophil activation test (BAT) with PEG and various COVID-19 vaccines. Interestingly, vaccination with the COVID-19 vaccines Janssen (Ad26.COV2.S; Janssen-Cilag) and Comirnaty (BNT162b2; BioNTech), which contained polysorbate and PEG, respectively, were well tolerated.

The patient's clinical history showed that she developed generalized itching, swelling of the hands and feet, laryngeal edema, and acute dyspnea after oral administration of Moviprep (containing PEG, molecular weight of 3350). Symptoms resolved quickly after intravenous administration of prednisolone and antihistamine by her general practitioner. Likewise, symptoms occurred a few minutes after the administration of several drugs (ibuprofen, pantoprazole, novamine sulfone, and oxycodone), of which the original compositions were unknown. Furthermore, she experienced a similar reaction about 4 hours after taking Magnesium Verla, which contains PEGs with a molecular weight of 6000 and 35 000 as excipients. Diagnostic measures comprised both laboratory tests (total IgE, 419 kU/L; specific IgE for latex, ethylene oxide, disinfectant,  $\alpha$ -gal all CAP class 0, tryptase, 4.19  $\mu$ g/L) and skin tests. Skin prick tests with PEG 6000 (1:100 dilution) and PEG 3350 (1:10), as well as intradermal tests (IDT) with polysorbate 80 (1:100), yielded positive results (Table, supplementary fig. 1a). Furthermore, IDT with Vaxzevria (AstraZeneca) and Janssen (both containing polysorbate 80), but not with Comirnaty (all 1:100), were positive. A BAT performed to further examine these findings yielded positive results to PEG 2000 (lipid component), Comirnaty, and Vaxzevria (supplementary fig. 1b). Therefore, taking into account her history of anaphylactic reactions to

Table. Results of Different Tests With Drug Excipients and COVID-19 Vaccines

| Substance, MW             | SPT reactivity, mm |      |           | IDT reactivity, mm | BAT | Challenge        |
|---------------------------|--------------------|------|-----------|--------------------|-----|------------------|
|                           | 1:100              | 1:10 | Undiluted | 1:100              |     |                  |
| <b>Excipients</b>         |                    |      |           |                    |     |                  |
| Polysorbate, 80           | N/P                | Neg  | Neg       | 6                  | Neg | N/P              |
| PEG, 400                  | N/P                | N/P  | Neg       | N/P                | N/P | N/P              |
| PEG linear, 2000          | Neg                | Neg  | Neg       | Neg                | Neg | N/P              |
| PEG lipid component, 2000 | N/P                | N/P  | N/P       | N/P                | Pos | N/P              |
| PEG, 3350 <sup>a</sup>    | N/P                | 5    | N/P       | N/P                | N/P | N/P              |
| PEG, 6000                 | 5                  | N/P  | N/P       | N/P                | Neg | N/P              |
| <b>COVID-19 vaccines</b>  |                    |      |           |                    |     |                  |
| BNT162b2 Comirnaty        | Neg                | Neg  | Neg       | Neg                | Pos | Neg <sup>b</sup> |
| AZD1222                   |                    |      |           |                    |     |                  |
| Vaxzevria                 | Neg                | Neg  | Neg       | 7                  | Pos | N/P              |
| Ad26.COV2.S Janssen       | Neg                | Neg  | Neg       | 10                 | Neg | Neg <sup>c</sup> |

Abbreviations: BAT, basophil activation test; IDT, intradermal test; Neg, negative; N/P, not performed; Pos, positive; SPT, skin prick test.

<sup>a</sup>Includes tests with Movicol and Macrogol

<sup>b</sup>Tolerated titrated vaccination (35%/65%)

<sup>c</sup>Tolerated titrated vaccination (10%/30%/60%)

PEG-containing drugs and the positive skin test and BAT results (Table), we assumed that she had experienced a hypersensitivity reaction to PEG and immunologic cross-reactivity to polysorbate 80.

PEG is found either as an active ingredient in laxatives (owing to its hygroscopic activity) or as a stabilizing or solubilizing additive in various drugs, including the COVID-19 vaccines Comirnaty and Spikevax [5-9]. Polysorbate 80, which is an excipient in a variety of drugs, including the COVID-19 vaccines Janssen and Vaxzevria, is a potential cross-allergen. Thus, vaccination with one of the 4 currently available COVID-19 vaccines entailed an unpredictable risk of anaphylaxis for the patient. However, in order to provide the patient with protection against COVID-19 infection, we decided in mutual agreement with her to perform fractionated vaccination with the polysorbate-containing COVID-19 vaccine Janssen (Ad26.COV2.S). Thirty minutes after receiving 4 mg of intravenous dimethindene maleate as premedication, the patient received 0.05 mL (10%), 0.15 mL (30%), and 0.3 mL (60%) of the vaccine intramuscularly (cumulative volume 0.5 mL), with 10 minutes between the respective applications. The vaccine was well tolerated. Encouraged by this outcome, we decided to administer a recommended booster vaccination 6 months later with Comirnaty, which contains PEG as a lipid component. Following the same injection regimen, the fractionated intramuscular vaccination was applied, with no adverse reactions (Table).

Our results are noteworthy in several ways. First, they confirm data from a study by Wolfson et al [10], who showed that PEG- or polysorbate-containing COVID-19 vaccines can be applied safely in most patients whose history and positive skin test results suggest that they are allergic to these excipients. Moreover, and extending beyond these investigational findings, we show that this observation also holds true for positive skin and in vitro test results with the vaccine itself. This outcome questions the significance of skin and in vitro test results with PEG, polysorbate, and the vaccines containing these additives. However, as the vast majority of the patients investigated by Wolfson et al and individuals tested in our department during the last 11 months had negative skin test results for PEG of various molecular weights, polysorbate 80, and the different COVID-19 vaccines, we do not believe the findings we report resemble nonspecific, irritative reactions. Tolerability could be affected by premedication, dosage, formulation, route, and/or the route of application of the vaccine. In conclusion, we suggest that when patients with potential hypersensitivity to the vaccine or its excipients receive the COVID-19 vaccine, appropriate attention should be given to safety measures, such as preventive premedication with antihistamines, emergency monitoring, and fractionated administration.

#### Funding

The authors declare that no funding was received for the present study.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ Manuscript received December 28, 2021; accepted for publication February 28, 2022.

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