Fractional Dosing of the Comirnaty Vaccine in 2 Patients With Immediate Acute Urticaria After the First Dose

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Since vaccination against SARS-CoV2 began in Spain on December 27, 2020, the Spanish Agency for Medicines and Medical Devices (AEMPS) has received 1537 reports of adverse events with Comirnaty [1]. Eight cases (0.52%) involved anaphylaxis. In 63% of cases, symptoms began within the first 30 minutes after vaccination (63%), and 75% of patients required epinephrine. The European Academy of Allergy and Clinical Immunology (EAACI) and the Spanish Society of Allergy and Clinical Immunology (SEAIC) have contraindicated Comirnaty only in patients who have had an allergic reaction to a previous dose or to any of its components [2-4].

Polyethylene glycol (PEG), one of the components of the Pfizer-BioNTech vaccine (Comirnaty), is considered a possible cause of allergic reactions, although this has not yet been confirmed [5].

PEG2000 is an excipient of the Comirnaty vaccine and is part of the lipid nanoparticle on which the mRNA is transported to ensure its preservation. PEGs are hydrophilic polymers with the ability to sensitize, as demonstrated in cases of immediate-type hypersensitivity associated with a molecular weight range of 300 to 20 000 g/mol [6]. PEG2000 is widely used as an excipient in products of daily use, including medicines, cosmetics, and food, although this is the first time PEG has been included as an excipient in a vaccine. PEG2000 differs from other excipients in its molecular weight and by the fact that it is coformulated as a stabilizing portion of a liposome [7].

The first case of allergic contact dermatitis due to PEG was described in 1978 [8], although it was not until 2008 when the first cases of immediate allergy [9] (including anaphylaxis) were reported. In recent years, many PEG-induced allergic reactions have been described [6,10].

Vinalopó University Hospital in Elche, Alicante, Spain began vaccinating its staff with the Comirnaty vaccine on January 8, 2021. Of the 1136 doses administered, there were 2 cases of immediate urticaria within the first 20 minutes after administration, that is, an incidence of 0.18%. One of the patients had a systemic reaction (patient 1) and the other a local reaction affecting the neckline (patient 2).

Patient 1 was a 57-year-old woman with a history of allergy to quinolones, mild intermittent pollen rhinitis, and recurrent acute urticaria with a negative allergology study, tryptase included.

Patient 2 was a 40-year-old man with a history of adverse reaction to cephalosporin and acetylsalicylic acid, mild intermittent asthma due to mites, and recurrent acute urticaria with a negative allergology study result, tryptase included.

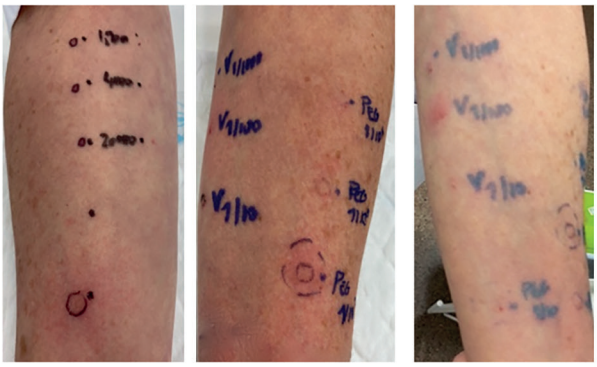
Both were treated with oral antihistamines, and patient 1 also received systemic intramuscular corticosteroids (methylprednisolone 60 mg). The reaction resolved in less than 1 hour in both patients.

Considering the recommendations of the EAACI [11], as well as our experience with adverse reactions with other vaccines [12], we carried out a complete allergology study in both patients following the diagnostic-therapeutic algorithm summarized in the Figure. The same skin tests were performed with the vaccine and PEGs on 5 healthy controls and yielded negative results.

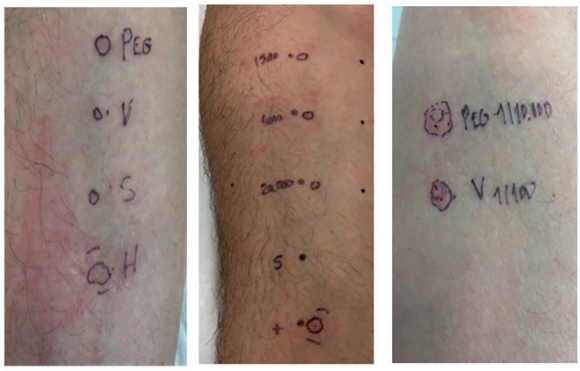
A basophil activation test (BAT; Basotest, Glycotope Biotechnology) [13] was carried out with the COVID vaccine (Comirnaty, as is and 3 additional serial 1/10 dilutions), and PEG 400, 1500, 4000, and 20 000 (Merck, at 10 mg/mL and 5 serial 1/10 dilutions). The cut-off was set at 5% CD63 induction over the negative control. BAT with Comirnaty was negative in both patients at all tested dilutions. Patient 2 showed weak positive results with PEG 400 (0.01 mg/mL, 10%; and 0.001 mg/mL ,7%), PEG 4000 (1 mg/mL, 7%), and PEG 20 000 (0.001 mg/mL, 9%). The results for the healthy controls were negative.

The study of hypersensitivity reactions with possible involvement of PEG is complicated by the difficulties in setting up specific IgE assays; therefore, the diagnostic work-up is generally limited to in vivo tests. PEG may induce the production of IgG and IgM antibodies both in patients who experience PEG-related adverse effects and in healthy individuals [13,14]. These antibodies may also mediate immune reactions to PEG involving activation of the complement system. PEG compounds are usually linear

Patient 1



Patient 2



NEGATIVE RESULTS	POSITIVE RESULTS
• Prick test with vaccine • ID with vaccine 1/1000 and 1/10 • Prick test with PEG 400 • 1 D with PEG 400 1/10 000 and 1/1000 • BAT with vaccine and PEG 400, 1500, 4000, and 20 000	• ID with vaccine 1/100 (late reading) (papule 6×3 mm) • ID with PEG 400 1/100 (papule 7×6 mm, erythema 16×18 mm) • Prick test with PEG 1500, 4000, and 20 000 (papules 4×3 mm)

NEGATIVE RESULTS	POSITIVE RESULTS
• Prick test with vaccine • BAT with vaccine • BAT with PEG 1500	• ID with vaccine 1/1000 (papule 4×5 mm, erythema 6×7 mm) • Prick test with PEG 400 (papule 3×2 mm), 1500 (papule 4×5 mm), 4000 (papule 4×4 mm), and 20 000 (papule 3×3 mm) • ID with PEG 400 1/10 000 (papule 5×5mm, erythema 11×9 mm) • BAT with PEG 400, 4000, and 20 000

Figure. Results of the study.

or branched polymers. The epitope of PEG is not known, and the allergenic capacity of this excipient is heterogeneous [6].

Given the positive results obtained in the study by prick and intradermal testing for both patients, the compatible symptoms with an immediate allergic reaction, the need to safely receive the second dose, and the lack of previous experience with Comirnaty, we decided to administer the vaccine using fractional dosing with premedication. First, the patient received methylprednisolone 60 mg IV, dexchlorpheniramine 5 mg IV, ranitidine 150 mg IV, and oral montelukast 10 mg. The second dose of Comirnaty was administered 30 minutes later divided into 3 doses of 0.1 mL, with an interval of 1 hour between doses and an additional 1 hour of observation after the last dose administered. Both patients experienced itching without hives 20 minutes after the first and second doses. This resolved spontaneously before administration of the following dose. All doses were completed without immediate or late incidents.

In conclusion, fractional dosing of the second dose of Comirnaty vaccine proved useful in 2 patients with an immediate allergic reaction during administration of their first dose.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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