Immediate-Type Hypersensitivity to Polyethylene Glycol (PEG) and a PEG-Containing COVID-19 Vaccine Revealed by Intradermal Testing

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The COVID-19 pandemic has had a huge effect on the way we have lived our lives since late 2019. The first vaccines, ie, BNT162b2 (BioNTech/Pfizer) and mRNA-1273 (Moderna), were approved in December 2020, setting off worldwide vaccination programs. As case series of anaphylaxis have been reported in association with administration of one or the other vaccine and drug excipients such as polyethylene glycol (PEG) came into focus as a potential trigger, the risk of anaphylaxis elicited by these vaccines in individuals with a history of (potential) immediate-type allergy to PEG (or other additives) has been intensively discussed [1-4]. We report the case of a patient who experienced anaphylaxis after administration of PEG-containing drugs and after intradermal testing (IDT) with the PEG-containing BNT162b2 vaccine.

A 24-year-old woman came to our department with anaphylactic episodes after exposure to various drugs. Shortly after oral intake of metamizole and sultamicillin tablets, she developed numbness in her hands, generalized pruritus, flushing, angioedema, dyspnea, and weakness before finally losing consciousness. A similar event occurred after extensive topical application of diclofenac ointment. She also had allergic rhinoconjunctivitis. Her daily medication consisted of oral hormonal contraception and occasional intake of ibuprofen tablets, which were well tolerated.

Laboratory analysis revealed serum IgE of 109 kU/L (with no IgE-mediated sensitization to ß-lactams [ie, penicilloyl G and V, ampicilloyl, amoxicilloyl], α-galactosidase, or ethylene oxide) and serum mast cell tryptase of 2.3 µg/L (all Thermo Fisher Scientific). For more detailed information on serum IgE analysis and allergen provocation tests, see the Online Repository at www.jiaci.org. Skin prick tests (SPTs) with individual pharmaceutical products yielded positive results to ibuprofen, metamizole, and penicillin V, but not to other nonsteroidal anti-inflammatory drugs or ß-lactams. Notably, some results were not in accordance with the patients' history of potential hypersensitivity to the active ingredients of the drugs (Table).

At that time, the patient experienced another anaphylactic reaction characterized by lip angioedema, dizziness, and dyspnea within minutes after inadvertent ingestion of a spoonful of yogurt mixed with a laxative for toddlers containing macrogol (PEG) with a molecular weight (MW) of 4000. The results of SPT with this compound were positive, and a comprehensive inspection of all previously tested medications revealed that she had had a positive SPT result only to drugs containing PEG with a higher MW (Table E1), thus indicating clinically relevant immediate-type sensitization to PEG. Accordingly, subsequent oral challenges with tablets containing the corresponding active substances but not PEG were all tolerated. PEG serves as a solvent and as a stabilizer in various pharmaceutical products, including the recently approved COVID-19 mRNA vaccines. Thus, the diagnostic work-up was extended to one vaccine containing PEG2000 (BNT162b2) and another comprising polysorbate 80 as a PEG–cross-reactive ingredient (AZD1222, COVID-19 vaccine, AstraZeneca), as well as various vaccine excipients (Table). While SPT was positive only to PEG6000, IDTs with the respective substances performed on consecutive days were positive for both vaccines (Figure E1). Shortly after administration of BNT162b2, the patient experienced itching on the palate and inner thighs, dizziness, and shortness of breath requiring intravenous treatment with antihistamines and corticosteroids.

PEG is used as additive in a variety of products, including drugs (both for injection and oral administration), laxatives, and lozenges, although it can also be found in numerous everyday articles such as cosmetics and personal care products, which make use of its stabilizing, solubilizing, or hygroscopic properties [5-10]. There have been several

Table. Titrated Skin Testing With Drug Excipients and COVID-19 Vaccines

Substance, MW	SPT reactivity, mm					IDT reactivity, mm
	1:10 000	1:1000	1:100	1:10	Undiluted	1:100
Polysorbate, 80	Neg	Neg	Neg	Neg	Neg	Neg
PEG, 400	Neg	Neg	Neg	Neg	Neg	NP
PEG, 2000	Neg	Neg	Neg	Neg	Neg	Neg
PEG, 6000	Neg	Neg	3	6	15	NP
COVID-19 vaccines						
BNT162b2	Neg	Neg	Neg	Neg	Neg	11[a]
AZD1222	Neg	Neg	Neg	Neg	Neg	10

Abbreviations: IDT, intradermal test; MW, molecular weight; NP, not performed; SPT, skin prick test.
[a]Compare with Figure E1, followed by a systemic reaction.

reports of hypersensitivity reactions to PEG [6,9,11]. With MWs ranging from 200 to 35 000 g/mol, higher-MW PEG is more likely to be associated with immediate-type reactions, which potentially lead to severe anaphylaxis, while lower MWs are more likely to elicit late-type contact dermatitis [6]. Our data show that SPT results were only positive for PEG or PEG-containing drugs with an MW of 4000 or higher, thus supporting the hypothesis that the probability of immediate-type reaction increases with MW. However, systemic exposure to skin test–negative PEG with lower MWs may still result in anaphylaxis [7], in the same way as the patient we report reacted to sultamicillin containing PEG2000. Notably, IDT with the PEG2000 BNT162b2 vaccine led to both a positive skin test and anaphylactic symptoms, pointing not only to the higher sensitivity of IDT, but also to differences in the reactivity of PEG depending on its presentation as an antigen, as it is bound to nanoparticles in the vaccine [4].

Expert consensus statements have provided guidelines for resource-oriented diagnostic and therapeutic procedures used in COVID-19 vaccination in patients with allergic diseases [1,8], and it has been suggested that patients with a history of anaphylaxis by unknown drugs or of idiopathic origin should undergo an allergology work-up before vaccination [8]. As the present case underlines, anaphylaxis to different classes of drugs should raise suspicion of an immediate-type allergy to excipients such as PEG [9]. Secondly, comprehensive testing is required to reveal potential allergens. This includes SPT with excipients such as PEG and polysorbate, as well as with the vaccines, if available. High-MW PEG should be included to increase sensitivity [6,7]. In terms of negative or indefinite results, titrated IDT should be performed with substances that are suitable for this purpose, after cautiously weighing up the risks and benefits. To avoid false-positive, irritative skin reactions, the vaccines applied should not exceed concentrations of 1:100 [12]. Still, the risk of eliciting systemic reactions by IDT must be borne in mind, as serious and, occasionally, fatal anaphylactic reactions have been reported [6].

Considering the urgent need for successful COVID-19 vaccination in as many people as possible and its very low potential for eliciting anaphylaxis, we agree with recent statements advising not to overdiagnose the risk of anaphylaxis [2]. However, as illustrated here, allergists must be alert and careful if they are to correctly identify individuals potentially at risk of severe allergic reactions and be aware of the pitfalls of skin testing with PEG and PEG-containing drugs when seeking to implement appropriate diagnostic measurements and ensure reasonable interpretation of results. Given that polysorbate-containing vaccine (AZD1222) yielded positive IDT results of unknown clinical relevance in the case we report, we recommend fractionated administration of AZD1222 (10%, followed by 90% 30 minutes later) in the emergency setting.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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