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

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While the COVID-19 pandemic has kept the world breathless since late 2019, the first vaccines, i.e. BNT162b2 (BioNTech/Pfizer) and mRNA-1273 (Moderna), have been 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 like polyethylene glycol (PEG) came into focus as 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 here report a patient who experienced anaphylaxis both after administration of PEG-containing drugs and intradermal testing (IDT) of the PEG-containing BNT162b2 vaccine.

A 24-year-old female presented to our department revealing anaphylactic episodes after exposure to different drugs. In particular, shortly after oral intake of metamizole and sultamicillin comprising tablets, respectively, she developed numbness of her hands, generalized pruritus, flushing, angioedema, dyspnea, weakness and finally collapsed. A similar event occurred after large scale topical application of a diclofenac containing ointment. In addition, she suffered from allergic rhinoconjunctivitis. Her daily medication consisted of oral hormonal contraception and occasional intake of ibuprofen tablets, which were well tolerated.

Laboratory analysis showed serum IgE of 109 kU/L with no IgE sensitization to betalactams (i.e. penicilloyl G and V, ampicilloyl, amoxicilloyl), alpha-galactosidase and ethylene oxide, and a serum mast cell tryptase of 2.3µg/L (all Thermo Fisher Scientific, Uppsala, Sweden).For more detailed information on serum IgE analysis and allergen provocation tests see this article's Online Repository at www.jiaci.org. Skin prick tests (SPT) with individual pharmaceutical products yielded positive results to ibuprofen, metamizole and penicillin V, but not to different other non-steroidal anti-inflammatory drugs and betalactams. Notably, some results were not in accordance with the patients' history of potential hypersensitivity to the active ingredients of the drugs (Table 1).

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At that time, she developed another anaphylactic reaction with lip angioedema, dizziness and dyspnea within minutes after inadvertent ingestion of a spoon full of yogurt mixed with a laxative for toddlers consisting of macrogol, i.e. PEG with a molecular weight (MW) of 4,000.SPT with this compound was positive, and comprehensive inspection of all formerly tested medications revealed that she had developed positive SPT only to drugs containing PEG of 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 solvent and stabilizerin various pharmaceutical products including the recently approved COVID-19 mRNA vaccines. Thus, 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 (Table1).While SPT was positive only to PEG6000,IDTwith the respective substances performed on consecutive days were positive for both vaccines (Figure E1).Shortly after administration of BNT162b2, the patient felt itching at the palate and between the legs, dizziness and shortness of breath, requiring intravenous treatment with antihistamines and glucocorticoids.

PEG issued as additive in a variety of products including different drugs(both for injection or oral uptake), laxatives and lozenges, but also numerous everyday articles like cosmetics or personal care products, among others making use of its stabilizing, solubilizing or hygroscopic properties[5-10]. There have been several reports of hypersensitivity reactions to PEG[6, 9,11]. With MW ranging from 200 to 35,000g/mol, PEG of higher MW are rather associated with immediate-type reactions potentially leading to severe anaphylaxis, while lower MW are more likely to elicit late-type contact dermatitis[6]. Our data shows, that SPT were only positive for PEG or PEG-comprising drugs with a MW of 4,000 or higher supporting the hypothesis that immediate-type reactivity rises with increasing MW. However, systemic exposure to skin test negative PEG with lower MW may still result in anaphylaxis[7], just as our patient reacted to sultamicillin containing PEG2000. Notably, IDT with the PEG2000 BNT162b2 vaccine led to both a positive skin test and anaphylactic symptoms, pointing to the higher sensitivity of IDT but also different PEG reactivity relying on its presentation as an antigen, as it is bound to nanoparticles in the vaccine [4].

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Expert consensus statements have been released providing guidelines for resource-oriented diagnostic and therapeutic procedures regarding COVID-19 vaccination in patients with allergic diseases [1,8]. Among others, it has been suggested that subjects with history of anaphylaxis by unknown drugs or of idiopathic origin should receive allergologic work-up before vaccination[8].As our case underlines, anaphylaxis to different substance 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 like PEG and polysorbate as well as 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 can be used for this purpose, cautiously weighing benefits and risks. To avoid false positive, irritative skin reactions, applied vaccines should not exceed concentrations of 1:100[12]. Still, the risk of eliciting systemic reactions by IDT has to be kept in mind, as serious, and in individual cases fatal, anaphylactic reactions have been reported [6].

Considering the urgent need of successful COVID-19 vaccination in as many people as possible and its overall very low potential of eliciting anaphylaxis, we agree with recent statements not to overdiagnose anaphylactic risks [2]. However, as illustrated here, as allergists we have to be alert and careful in correctly identifying individuals who may be at risk of severe allergic reactions and be well aware about pitfalls in skin testing with PEG and PEG-containing drugs for implementation of proper diagnostic measurements and reasonable interpretation of the retrieved results. For COVID-19 vaccination of our patient – as polysorbate yielded positive IDT of unknown clinical relevance – we would suggest fractionated administration of AZD1222 (10%, followed by 90% 30 min later) in an emergency setting.

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Conflict of interest

All authors declare there are no conflicts of interest.

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Tab. 1: Titrated skin testing with drug excipients and COVID-19 vaccines.

substance[MW]	**SPT reactivity [mm]**					**IDT reactivity [mm]**
	1:10,000	1:1,000	1:100	1:10	undiluted	1:100
polysorbate [80]	neg.	neg.	neg.	neg.	neg.	neg.
PEG [400]	neg.	neg.	neg.	neg.	neg.	N/P
PEG [2,000]	neg.	neg.	neg.	neg.	neg.	neg.
PEG [6,000]	neg.	neg.	**3**	**6**	**15**	N/P
COVID-19 vaccines						
BNT162b2	neg.	neg.	neg.	neg.	neg.	**11***
AZD1222	neg.	neg.	neg.	neg.	neg.	**10**

IDT – intradermal test; N/P – not performed; SPT – skin prick test

*cf. Figure 1; followed by a systemic reaction