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The role of skin tests with polyethylene glycol and polysorbate 80 in the vaccination campaign for COVID-19: results from an Italian multicenter survey

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Key words

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Impact statement

The study, consistently with the latest guidelines, demonstrates that after adequate diagnostic work-up, the positivity of skin test with PEG and or PS before vaccination is rare and mostly replaceable by an accurate clinical history.

Summary

Background. *International guidelines suggested skin tests with Polyethylene-glycol (PEG) and polysorbate 80 (PS-80), to investigate a possible hypersensitivity to these excipients either to identify subjects at risk of developing allergic reactions to COVID-19 vaccines, or in patients with suspected IgE mediated hypersensitivity reactions (HR) to the COVID-19 vaccine. The main purpose of this study was to investigate the prevalence of PEG and PS sensitization in patients with a clinical history of HR to drugs containing PEG/PS and in patients with a suspected COVID-19 vaccine immediate HR.* ***Methods.*** *This was a multicenter retrospective study conducted by allergists belonging to 20 Italian medical centers. Skin testing was performed in 531 patients with either a clinical history of suspected hypersensitivity reaction (HR) to drugs containing PEG and/or PS-80 (group 1: 362 patient) or a suspected HR to COVID-19 vaccines (group 2: 169 patient), as suggested by the AAIITO/SIAAIC guidelines for the "management of patients at risk of allergic reactions to COVID-19 vaccines".* ***Results.*** *10/362 (0.02%) had positive skin test to one or both excipients in group 1, 12/169 (7.1%) in group 2 ($p < 0.01$). In group 2 HRs to COVID-19 vaccines were immediate in 10/12 of cases and anaphylaxis occurred in 4/12 of patients.* ***Conclusions.*** *The positivity of skin test with PEG and or PS before vaccination is extremely rare and mostly replaceable by an accurate clinical history. Sensitization to PEG and PS has to be investigated in patients with a previous immediate HR to a COVID-19 vaccine, in particular in patients with anaphylaxis.*

Introduction

In December 2020, at the beginning of the COVID-19 vaccination campaign, 2 anaphylaxes were reported after the administration of the first 500 BNT162b2vaccines. For this reason, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) temporarily contraindicated this vaccine in patients with a severe allergic background (1).

This contraindication was revoked in January 2021 and more recent data on the safety of COVID-19 vaccines show that severe hypersensitivity reactions are rare even in patients with an allergic background (2-4).

In mRNA vaccines (Comirnaty by Pfizer BioNTech and Spikevax by Moderna) the components suspected of being the cause of IgE-mediated hypersensitivity reactions (HR) are the excipient Polyethylene glycol (PEG or macrogol, with a molecular weight of 2000 kDa) and Trometamol (contained at time only in Spikevax), while in the adenoviral vector vaccines (Vaxzeviria by AstraZeneca and Jcovden by Janssen) polysorbate 80 (PS-80), a substance chemically correlated with PEGs has been incriminated. Non-IgE mediated mechanisms with activation of immunological mechanisms triggered by complement activation (CARPA, Complement Activation-Related PseudoAllergy) have also been hypothesized (5).

According to current national and international guidelines, an allergological evaluation in still needed in individuals with suspected hypersensitivity to excipients of COVID-19 vaccines, PEG and PS-80.

An evaluation by allergy specialist is recommended also in patients with a suspected HR to COVID-19 vaccination, in order to evaluate the indication to a further vaccine dose and which vaccine could be administered (5-7).

According to the aforementioned guidelines, individuals with allergy to foods, inhalants, Hymenoptera venom and drugs (with the exception of PEG/PS containing injective drugs) can be vaccinated in a standard setting and don't need a "preventive" allergological evaluation.
Among these patients, even those with a history of anaphylaxis can be vaccinated in a standard setting with a prolonged observation period (60 minutes according to Italian guidelines).
Instead, an allergy evaluation is needed in subjects with a previous reaction to drugs containing PEG or PS. In these patients, skin tests with PEG and/or PS are suggested as a useful test to evaluate a possible contraindication to vaccination. Trometamol was contained at that time as an excipient only in Spikevax. This substance may have an irritative effect, and for this reason, is not recommended for skin testing.
In individuals with a severe anaphylactic reaction to prior doses of COVID-19 vaccines, both in case of positive and negative tests, it is preferable not to administer the following dose of the same vaccine.
It should be emphasized that data on skin tests currently available in the literature indicate their low positive and negative predictive value and the need for the diagnostic procedure to be entrusted to the allergy specialist.
These guidelines highlight the central role of allergist in the evaluation of subjects with suspected hypersensitivity to COVID-19 vaccines or to the excipients contained in these preparations.
The main purpose of this study was to investigate the prevalence of PEG and PS sensitization in Italian patients with a clinical history of HR to drugs containing PEG/PS and in patients with a suspected COVID-19 vaccine immediate HR.

Materials and methods

This was a multicenter retrospective study conducted, from March to December, 2021, by allergists belonging to 20 Italian medical centers located either in hospitals (n = 9) or outpatient clinics (n = 13).
Skin testing was performed in patients with either a clinical history of suspected hypersensitivity reaction (HR) to drugs containing PEG and/or PS 80 (group 1) or a suspected HR to COVID-19 vaccines (group 2), as suggested by the AAIITO/SIAAIC guidelines for the "management of patients at risk of allergic reactions to COVID-19 vaccines" (7).
Skin tests were performed in 6 steps: 3 steps for prick tests followed by 3 steps for intradermal tests using increasing concentrations of PEG and PS, as suggested by national and international guidelines (6, 7). Demographic and clinical data were collected: age, previous anaphylaxis or HR to drug or vaccine (either containing or not containing PEG and PS), allergic comorbidities. Data were collected by means of an anonymous survey, filled out online by an allergist. No data on gender and ethnicity were collected. The approval by the ethical committee was not requested being an anonymous survey.

Statistical analysis

Microsoft Excel 2019®, OpenEpi online (www.openepi.com, accessed on 25 January 2022), and JASP 0.16.0.0 were used for statistical analysis. The distribution of categorical variables among groups were compared using the chi-square test. Categorical variables are reported as absolute numbers (percentage). P-values < 0.05 were considered significant.

Results

531 patients were enrolled: 362 (68.2%) were referred to carry out the skin tests to exclude PEG/PS hypersensitivity before vaccination (group 1), and 169 (31.8%) for a suspected HR to the first or second dose of COVID-19 vaccine (group 2).
10/362 (0.02%) scored positive on skin test to one or both excipients in group 1 *vs* 12/169 (7.1%) in group 2 ($p < 0.01$). All patients of group 1 had a previous drug anaphylaxis and 50% had a previous HR to drugs containing PEG. In group 2, HRs to COVID-19 vaccines occurred after the first dose in all patients. HRs were immediate in 10/12 (83%) patients and anaphylaxis occurred in 4/12 (33%) patients.

Patients with a history of adverse reactions to drugs containing PEG

Demographic and clinical features

362 patients were enrolled. Patients between 40 and 70 years old represented the most numerous age group. 160 patients had a clinical history of anaphylaxis (128 induced by drugs, 15 by vaccines, and 6 by Hymenoptera stings). 41 patients (11,7%) had a clinical history of multiple anaphylaxis (≥ 2). Antibiotics, NSAIDs and vaccines were the most common causes of previous anaphylaxis. 50.6% (n = 179) had a clinical history of multiple drug reactions (most caused by antibiotics and NSAIDs). 165 patients reported adverse reactions to drugs or vaccines containing PEG (most commonly amoxicillin/clavulanate, paclitaxel, ciprofloxacin, methylprednisolone, and docetaxel).
253 (72.5%) showed allergic or pseudoallergic comorbidities (asthma, rhinitis, conjunctivitis, dermatitis, chronic spontaneous urticaria), and 60% of the population suffered from extra-allergological comorbidities (cardiovascular diseases, endocrinopathies, hyperuricemia, osteoporosis).

Characteristics of patients with positive skin test to PEG/polysorbate

10 patients scored positive on skin test with PEG and PS (**table I**): 2 patients (PT n. 204, 351) scored positive only to skin test with PS (antipneumococcus vaccine and Optive plus).

Table I *- Demographic and clinical features of patients with a clinical history of HRs to drugs containing polyethylene-glycol (PEG) or/and polysorbate (PS).*

PT	Age	Past anaphylaxis	Drug anaphylaxis	Multiple anaphylaxis	Multiple drugs reactions	Past reactions to PEG and or PS containing drugs	Tolerance to PEG containing drugs	Allergic comorbidities	AntiFlu vaccine	Positive skin test (PEG)	Positive skin test (PS)
9	71-80	Yes	Yes	Yes	Yes	Yes (Pantoprazole, amoxicillin/ clavulanate)		No	No	ID MPDa 0.04 mg/ml	
32	41-50	Yes	Yes	No	Yes	Yes (Cetrizine)			No	SPT Macrogol 1:1	
89	41-50	Yes	Yes (Lidocaine + MPDa)	No	Yes	No		Yes (Rhinitis, conjunctivitis)	No	SPT MPDa 40 mg/ml, ID MPDa 0.04/0.4/4 mg/ml	
168	41-50	Yes	Yes (Betamethasone)	No	No	No	Yes	Yes (asthma, rhinitis)	No	SPT MPDa 40 mg/ml, SPT MPD 40 mg/ml, ID MPD (control) 0.04/0.4/4 mg/ml, ID MPDa 0.04/0.4/4 mg/ml	
204	41-50	Yes	Yes	No	No	No			No		SPT and ID antipneumococcus vaccine
265	51-60	Yes	Yes	No	No	No		Yes (Rhinitis, conjunctivitis)	No	ID MPDa 0.4 mg/ml	
346	41-50	Yes	Yes	No	No	Yes (MPDa)	Yes	No	No	ID MPDa 4 mg/ml	SPT and ID Optive plus™
351	51-60	No	No	No	Yes			No	No		ID Optive plus™
359	51-60	Yes	Yes	No	No	Yes (Paclitaxel)			No	ID MPDa 0.4 mg/ml	ID Triam 4 mg/ml
360	61-70	Yes	Yes	No	No	Yes (Macrogol)	No		No	SPT Macrogol 1:1, SPT MPDa 40 mg/ml, ID MPDa 4 mg/ml	SPT Triam 40 mg/ml, SPT Optive plus™

PT: patient; PEG: polyethylene-glycol; PS: polisorbate; Triam: triamcinolone; MPDa: methylprednisolone acetate (Depomedrol®); MPD: methylprednisolone (Urbason).

3 patients (PT n. 346, 359, 360) scored positive on both PS (Kenacort® "Triamcinolone acetonide" and/or Optive plus) and PEG (Depomedrol® "Methylprednisolone acetate" and Macrogol) testing.
5 (PT n. 9, 32, 89, 168, 265) patients showed a PEG positive skin test (one with macrogol 1:1 on SPT, and the others ID with Depomedrol® (doubtful SPT result)).
Patient n. 168 scored positive on SPT with both to Depomedrol® "Methylprednisolone acetate" and Urbason® "Methylprednisolone", suggesting methylprednisolone rather than PEG hypersensitivity.
5 patients experienced a previous reaction to PEG-containing drugs (Cetirizine, Paclitaxel, Augmentin® "Amoxicillin/Clavunate", Pantoprazole, Movicol® "Macrogol").
3 patients showed allergic comorbidities (rhinitis, asthma, conjunctivitis).
9/10 patients had a clinical history of drug anaphylaxis: 1 patient to Depomedrol® and Lidocaine "Methylprednisolone acetate", 1 to Bentelan® "Betamethasone". The drug is not known for the other 7. mRNA vaccines have been discouraged to patient with PEG skin test positivity.

Patients with suspected hypersensitivity reactions to COVID-19 vaccines

Demographic and clinical features (**table IIA**)
A total of 169 patients with suspected hypersensitivity reactions to COVID-19 vaccine were registered in the participating centers and subsequently submitted to skin testing with vaccine excipients (7). 14% of subjects had a clinical history of allergic reactions at least to 2 different drugs and 17% had a clinical history of anaphylaxis. Other allergic comorbidities were reported in 57% of subjects. Among patients with previous anaphylaxis there was a significantly higher percentage of subjects with positive skin tests than in patients without anaphylaxis (17% *vs* 5%, $p < 0.01$) while there was not a significative difference in patient with multiple drug hypersensitivity.

Details of the suspected HR (**table IIB**)
147/169 (95%) of suspected HRs to COVID-19 vaccines occurred after the 1st dose, 8/169 (4.7%) after the 2nd dose and 14/169 (8.2%) after both doses. This means that globally 22 patients had HRs after the 2nd dose. 104/161 (64%) of HRs

Table II - (A) *Demographic and clinical features of patients with HRs to COVID-19 vaccines;* ***(B)*** *Demographic and clinical features of patients with HRs to COVID-19 vaccines and positive skin tests.*

A

Clinical and demographic features	n	%
Age group	169	100
20-30	15	9
31-40	39	23
41-50	36	21
51-60	31	18
61-70	26	15
71-80	12	7
> 80	3	2
Previous anaphylaxis	29	17
Drug	9	5
Vaccine	13	8
> 1 anaphylaxis	5	3
> 1 drug HR	25	15
HR to PEG/ polysorbate containing drug	26	15
Allergic comorbidities	96	57
AntiFlu vaccine (2020/2021)	21	12

B

Clinical and demographic features	n	%
Age range	12	100
31-40	2	16.7
41-50	2	16.7
51-60	5	41.7
61-70	2	16.7
71-80	1	8.3
Past anaphylaxis	5	41.7
Drug anaphylaxis	4	33.3
Multiple anaphylaxis	3	25
Multiple drug reactions	3	25
Past reactions to PEG-containing drugs	4	33.3
Tolerance to PEG-containing drugs*	5	41.7
allergic comorbidities	5	41.7
AntiFlu vaccine	2	16.7

HR to anti-SARS-CoV-2 vaccines					
	n	**%**		**n**	**%**
HR D1	161	95	HR D2	19	18
Immediate	104	62	Immediate	13	68
Local reactions	8	8	Local reactions	5	26
Diffuse itching	41	39	Diffuse itching	5	26
Urticaria	14	13	Urticaria	2	11
Rash (other)	45	43	Rash (other)	7	37
Angioedema	41	39	Angioedema	4	21
Skin (total)	107	103	Skin (total)	12	63
Pharyngeal disclosure	17	16	Pharyngeal disclosure	2	11
Asthma/ bronchospasm	21	20	Asthma/ bronchospasm	4	21
Anaphylaxis/ glottic edema	11	7	Anaphylaxis/glottic edema	2	11
Paresthesia	28	27	Paresthesia	1	5
Drugs to treat HR	106	66	**Drugs to treat HR D2**		
AntiH1	89	86	Antih1	10	53
GC	65	63	Gc	8	42
Epinephrine	9	9	Epinephrine	2	11
			HR 1 and 2D	12	63
			Positive skin test	12	63

HRs to COVID-19 vaccine		
HR 1D	12	100
HR immediate	10	83.3
HR not immediate	2	16.7
HR: symptoms		
Local reactions	1	8.3

*Tolerance to PEG containing drugs before COVID-19 vaccines.

after first dose and 13/22 (68%) of HRs after 2nd dose were immediate (> time of onset within 4 hours from vaccination). Skin reactions were the most common HRs, occurring in 69.6% of patients. 12/169 of HR were classified as anaphylaxis according to modified WAO grading system (6). Antihistamines were used in 57% of cases, corticosteroids in 41%, and epinephrine in 11% of cases.

***Positive skin tests in patients with suspected hypersensitivity reactions* (table III)**

Among the 169 patients with suspected HRs, 12 (7.1%) had positive skin test results. 7 patients showed positive tests for PEG (PT n. 1, 3, 4, 5, 8, 11, 12) and 3 for PS (PT n. 2, 6, 10), while only 2 (PT n. 7, 10) patient had positive tests for both excipients.

In this subgroup HRs to COVID-19 vaccines occurred after the first dose in all patients.

HRs were immediate in 10/12 (83%) of cases and anaphylaxis occurred in 4/12 (33%) of patients.

5/12 (41%) had both a history of anaphylaxis and allergic comorbidities.

Only 2 patients out of 12 received the 2nd dose of vaccine:

Patient n. 8 received the 2nd dose of the same vaccine (BNT162b2) despite HR to the first dose and reported the same reaction (dyspnea and bronchospasm).

Patient n. 12, who developed a generalized urticaria after the first dose of mRNA vaccine and was positive to PEG received the 2nd dose with adenoviral vaccine, administered in fractioned doses, reported no adverse events.

Considering the medical history of those patients, 4/12 (33%) reported past reactions to PEG-containing drugs, while 5/12 (41,7%) reported, before COVID-19 vaccination, the tolerance of at least one PEG- containing drug. HRs to PEG- containing vaccines in subjects who tolerated PEG- containing drug could be explained by the role of lipidic nanoparticles. Those nanoparticles, when conjugated to PEG, may determine an HR mediated by complement activation.

Discussion

The study, consistently with the latest national and international guidelines (1, 2) demonstrates that after adequate diagnostic work-up, the positivity of skin test with PEG and or PS before

Table III *- Patients with positive skin tests and hypersensitive reaction to COVID-19 vaccine.*

Patient	Age	Previous anaphylaxis	Allergic comorbidities	HR 1D	Type of vaccine	Time of onset	Therapy of HR	Received 2nd dose	HyPR2D	Time of onset	Therapy HyPR2D	Positive skin test (PEG)	Positive skin test (polysorbate)
1	51-60	No	No	Local wheal and rush, angioedema	ND	< 1 h	AntiH1, GCs	ND	No	NA	NA	Macrogol 3350 ID 0.4 mg/ml	No
2	61-70	vaccine	ACD	Angioedema, dyspnea, bronchospasm (A)	ND	< 1 h	Epi	ND	No	NA	NA	No	p80 Triam ID 0.4 mg/ml
3	51-60	Food	Drugs allergies	Pharyngeal discomfort, mouth paresthesia	ND	< 1 h	GCs	ND	No	NA	NA	MPD ID 40 mg/ml	No
4	31-40	Other drugs	Rhinoconjuctivitis	Apnea, bronchospasm, anaphylaxis without hypotension (A)	ND	< 1 h	Epi	ND	No	NA	NA	SPT Macrogol 3350 1:10, SPT MPDa 40 mg/ml	No
5	51-60	No	No	Diffuse itching, mouth paresthesia	ND	< 1 h	AntiH1, GCs	ND	No	NA	NA	SPT Macrogol 3350 1:10, ID MPDa 0.4 mg/ml, ID MPDa 4 mg/ml	No
6	41-50	No	No	Angioedema, dyspnea, bronchospasm (A)	Adenovirus (ChAdOx1 nCoV-19)	1-4 h	AntiH1, GCs	ND	No	NA	NA	No	SPT p80 Triam 40 mg/ml, ID p80 Triam 40 mg/ml
7	71-80	No	No	Angioedema, glottic edema (A)	ND	< 1 h	AntiH1, GCs	ND	No	NA	NA	SPT Macrogol 3350 1:10	ID p80 Triam 0.4 mg/ml
8	51-60	vaccine, other drugs	Asthma	Dyspnea, bronchospasm	mRNA (BNT162b2)	< 1 h	Epi	yes, mRNA (BNT162b2)	Dyspnea, bronchospasm	< 1	AntiH1, GCs	SPT Macrogol 3350 1:100	No
9	61-70	No	No	Angioedema	Adenovirus (ChAdOx1 nCoV-19)	> 4 h	AntiH1, GCs	ND	No	NA	NA	No	ID p80 eye drops 1:10

Patient	Age	Previous anaphylaxis	Allergic comorbidities	HR 1D	Type of vaccine	Time of onset	Therapy of HR	Received 2nd dose	HyPR2D	Time of onset	Therapy HyPR2D	Positive skin test (PEG)	Positive skin test (polysorbate)
10	31-40	No	No	Urticaria, itching	ND	> 4 h	AntiH1, GCs	No	NA	NA	NA	ID MPDa 0.4 mg/ml	ID p80 eye drops 1:11
11	51-60	Other drugs	Rhinoconjuctivitis	Diffuse itching, angioedema, maculopapular rash, hypotension, dyspnea, bronchospasm, rhinitis (A)	mRNA (BNT162b2)	< 1 h	AntiH1, GCs, Epi	ND	No	NA	NA	ID MPDa 4 mg/ml	No
12	41-50	No	No	Urticaria	mRNA (BNT162b2)	< 1 h	ND	Yes*	No	NA	NA	SPT Macrogol 3350 1:100	No

PT: patients; HR: hypersensitivity reactions; antiH1: antihistamines; GCs: glucocorticoids; Epi: epinephrine; ID: intradermal; SPT: skin prick test; Triam: triamcinolone; MPDa: methylprednisolone acetate; (A): anaphylaxis; ND: no data, NA: not applicable; *adenovirus vaccine, fractioned doses.

vaccination is extremely rare and mostly replaceable by an accurate clinical history. In particular, we found a significatively lower prevalence of positive skin tests in group 1 than in group 2. Sensitization to PEG and PS has to be investigated in patients with a previous immediate HR to a COVID-19 vaccine, in particular in patients with anaphylaxis. Nonetheless, it is important to underline that the vast majority of patients who experience a suspected HR at the first dose of COVID-19 vaccine should not be automatically precluded from being re-vaccinated, in particular in patients with non-severe reactions and negative test, after an accurate allergological evaluation. This is also underlined by the latest Italian guidelines and recent review and meta-analysis of the available literature regarding immediate reactions to the first dose of COVID-19 vaccine, where the incidence of severe immediate reactions to re-vaccination with the second dose of COVID-19 vaccine was very low (0.16%) in the absence of related deaths (3, 7, 8). From our data, patients with previous anaphylaxis have also a major probability of scoring positive on skin tests. This further supports the importance of a complete anamnesis in the screening and management of these reactions. Only patients who received a new diagnosis of allergy to PEG/PS, ascertained by skin test, would not be suitable for the administration of the second dose. On this point, the Italian guidelines highlight the fact that skin tests seem to have a low positive and negative predictive value (9).

In addition to considering excipients as the cause of IgE-mediated allergic reactions to the currently approved COVID-19 vaccines, alternative non-IgE pathways for activating mast cells and other inflammatory cells must be considered, because they can lead to a similar clinical presentation. For example, activation of the complement system leads to the generation of C3a, C4a, and C5a, which are potent activators of inflammation and are called anaphylatoxins due to their ability to cause non-IgE-mediated mast cell degranulation (1).

Depletion of complement levels and production of C3a and C5a have been seen in both mouse models of anaphylaxis and in clinical studies. C5a is the most potent anaphylatoxins and can contribute to vascular permeability as well as activation and chemotaxis of neutrophils, basophils, and mast cells. Infection and tissue injury can lead to activation of the complement system resulting in the generation of C3a and C5a, and these mediators can lead to anaphylaxis. PEG IgM and IgG can cause complement-activation-related pseudoallergy, a nonspecific immune response to PEGylated, nanoparticle-based medicines (1).

Clearly, it is important to consider both IgE and alternative mechanisms for the current reactions. Measurement of serum tryptase and complement may help elucidate the mechanism of the drug-induced reactions in patients following COVID-19 vaccination (1).

For this reason, the panel of experts suggests not to limit the allergy evaluation to the result of skin tests, but to carry out an

integrated evaluation for each patient based on: 1) the precise allergological history, 2) the severity of the reported reactions, and 3) the evaluation of the risk/benefit ratio deriving from vaccination (SIAAIC/AAIITO).

In conclusion, the survey demonstrates that the onset of symptoms suggestive for a HR to the first dose of COVID-19 vaccine should not automatically prevent the citizen from receiving the second dose but requires an adequate allergy assessment that include a detailed clinical history associated with skin tests, when indicated by the allergist.

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Contributions

The authors contributed equally to this work.

Conflict of interests

The authors declare that they have no conflict of interests.

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