

The Polysorbate containing AstraZeneca COVID-19 vaccine is tolerated by polyethylene glycol (PEG) allergic patients

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Abstract

Background: Polyethylene glycol (PEG) is the excipient found in the mRNA COVID-19 vaccines. We previously demonstrated PEG allergy was a cause of severe anaphylaxis to the Pfizer/BioNTech COVID-19 vaccine. PEG is widely used in many household products, cosmetics and medicines. However PEG allergy is rare, there have been few confirmed cases of PEG allergy. The excipient of potential concern in the AstraZeneca COVID-19 vaccine is polysorbate 80 (PS80). Cross-reactivity between PEG and polysorbate has been suggested, based on their composition and skin-test data. The aim of this study was to determine whether PEG-allergic patients could be vaccinated with the PS80 containing AstraZeneca COVID-19 vaccine.

Method: Eight patients with PEG allergy were identified by the allergy clinic at Cambridge University Hospital. Patients underwent skin prick testing to PS80 (20%) and to the AstraZeneca COVID-19 vaccine prior to vaccination.

Results: All eight patients allergic to PEG tolerated the AstraZeneca COVID-19 vaccine, even in 2 patients where the PS80 skin prick test was positive and 1 with a positive skin prick test to the AstraZeneca COVID-19 vaccine.

Conclusion: Patients allergic to PEG, previously denied COVID vaccination, may now be safely vaccinated with the PS80 containing AstraZeneca vaccine and need only avoid the PEG-containing mRNA COVID-19 vaccines. This opens up the possibility that these patients will also tolerate other vaccines containing PS80 such as the Janssen/Johnson and Johnson COVID-19 vaccine. Clinical cross-reactivity between PEG and PS80 did not occur in this vaccine setting.

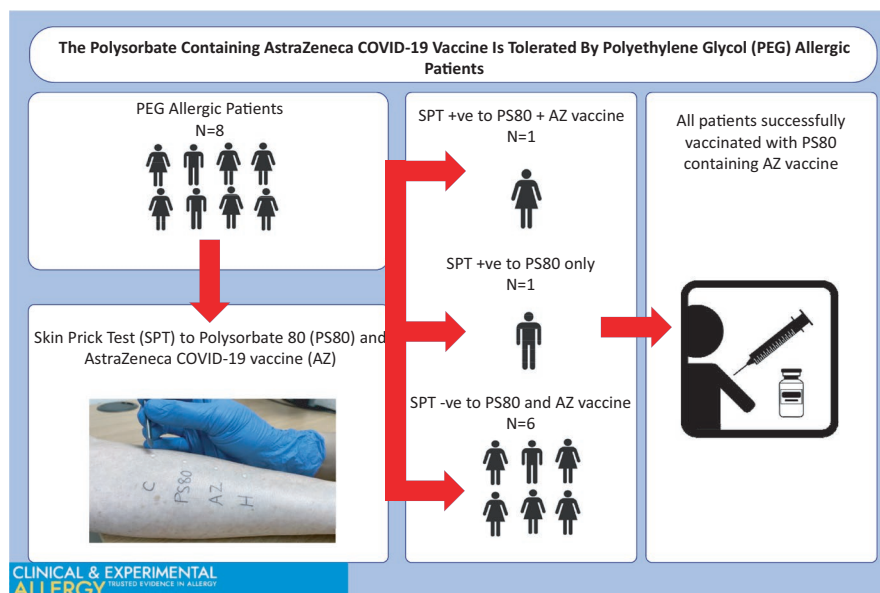
KEYWORDS

COVID-19, COVID-19 vaccines, drug allergy, PEG allergy, polysorbate 80

1 | INTRODUCTION

Suspected anaphylaxis to the COVID-19 vaccines in the UK is reported at a rate of about 11–17 per million doses for the Pfizer/BioNTech and AstraZeneca vaccines respectively [MHRA yellow card data, 23 June 2021]. This will underestimate the true size of the problem as cases are not reported and 43% of these data relate to second doses. However, after investigation, true allergy is rarely

found and many are not IgE mediated¹ and are often labelled immunogenic reactions. Recent studies have shown successful revaccination in patients who had suspected allergic reactions to their first dose.^{2,3} Polysorbate 80 (PS80) is the potentially allergenic excipient in the AstraZeneca and Janssen/Johnson and Johnson COVID-19 vaccines. PS80 is used as an excipient in many drugs (including some vaccines, e.g., some influenza vaccines) and as a food additive and is thus widely tolerated.⁴ There have been cases of clinical reactivity



GRAPHICAL ABSTRACT

The Pfizer/BioNTech COVID-19 vaccine contains polyethylene glycol (PEG), whereas the AstraZeneca vaccine contains polysorbate 80 (PS80). Cross-reactivity between PEG and PS80 has been suggested, based on their structural similarity. We show that 8/8 PEG-allergic patients tolerated the AstraZeneca vaccine, even in 2 patients where the PS80 skin prick test was positive. This suggests that PEG-allergic patients previously denied COVID vaccination, may now be safely vaccinated with the AstraZeneca vaccine and need only avoid the PEG containing mRNA COVID vaccines.

to PS80 which were non-IgE mediated,⁵ and a case report of IgE-mediated anaphylaxis to PS80.⁶ However, these cases are not in patients who have underlying polyethylene glycol (PEG) allergy. PEG is the known allergenic excipient in the mRNA COVID-19 vaccines, Pfizer/BioNTech and Moderna.⁴ The Pfizer/BioNTech and Moderna COVID-19 vaccines are therefore contraindicated in patients with PEG allergy.^{7,8}

The suggestion of cross-reactivity between PEG and PS80 arose because of their similar chemical structures. Stone et al. reported positive skin tests to triamcinolone acetonide (containing PS80)⁹ in 2 patients with confirmed PEG allergy. Garvey found 3 of 10 patients with PEG allergy had positive skin prick tests to PS80.¹⁰ However, the clinical correlation of these positive skin tests to PS80 remains to be established. There currently is no clear guidance on the management of these patients, with management differing between allergists.

We have previously reported the first confirmed case of PEG allergy following anaphylaxis to the Pfizer/BioNTech COVID-19 vaccine containing PEG.⁷ The aim of this study was to investigate whether patients with PEG allergy tolerate the AstraZeneca COVID-19 vaccine containing PS80.

2 | METHOD

Eight patients with PEG allergy were identified by the allergy clinic at Cambridge University Hospital between October 2013 and February 2021. Initial diagnosis was made following anaphylaxis to at least one PEG-containing drug with positive skin tests to PEG (6 skin prick tests (SPT) to PEG, 1 intradermal test to PEG and 1 SPT to Movicol).

Key Messages

- Cross-reactivity between PEG and polysorbate has been suggested, but the clinical correlate is not established.
- We show that 8/8 PEG-allergic patients (2/8 positive SPT to PS80) tolerated the AstraZeneca vaccine.
- Therefore, PEG-allergic patients can be safely vaccinated with the PS80 containing AstraZeneca vaccine.

Patients were offered vaccination with the AstraZeneca COVID-19 vaccine (<100 mcg of PS80 per dose⁴) in clinic. All patients underwent SPTs to PS80 (20%) and to the AstraZeneca COVID-19 vaccine prior to vaccination. IV access was obtained prior to vaccination. If a patient had positive SPT to PS80 and AstraZeneca vaccine, then a split dose was given. Patients were monitored for 1 h following vaccination in our drug allergy clinic with full access to anaphylaxis and resuscitation treatment. Blood pressure, heart rate and oxygen saturations were measured when the patient entered the drug allergy clinic, and at 30 min and 1 h into the challenge. Written informed consent was obtained from all patients.

3 | RESULTS

Eight patients were previously confirmed to have PEG allergy (2 males/6 females). Six of the patients had co-morbidities, with two of these patients being atopic (Table 1). Six of these patients have

TABLE 1 Summary of findings in PEG-allergic patients who tolerated the AstraZeneca COVID-19 vaccine

Age/Sex	Culprit agents	Symptoms	Comorbidities	PEG drugs tolerating	PEG ST (Concentration %) (Year of diagnosis)	PS80 SPT (20%) (W/F)	AZ vaccine SPT (neat) (W/F)	Tolerated AZ vaccine
52F	Pfizer/BioNTech COVID-19 vaccine (PEG 2000) Azithromycin (PEG 6000) Cosmetics	Coughing desaturation and increased RR. Profound hypotension Facial swelling, widespread urticaria and wheezing Urticaria	Hay fever	None	SPT PEG 4000 (1%) (2021)	Neg	Neg	Yes (1 dose, Pfizer/ BioNTech first dose)
23F	Methylprednisolone (PEG 3350) Penicillin V (PEG 6000) Cosmetics	Facial swelling, rhinitis, throat swelling and pre-syncopal Oral pruritus and wheezing Urticaria	Eczema Asthma Allergic rhinitis sensitised to dust mite and grass pollen	None	SPT PEG 8000 (1%) 20,000 (1%) Poloxamer 407 (10%) (2020)	Neg	Neg	Yes (2 doses)
55F	Medroxy-progesterone acetate (PEG 3350, Polysorbate 80) Moviprep (PEG 3350) Cosmetic	Generalised urticaria, presyncope Generalised urticaria Urticaria	None	None	SPT PEG 3350 (50%) PEG 8000 (0.1%) PEG 20,000 (0.1%) Poloxamer 407 (10%) (2016)	Neg	Neg	Yes (2 doses)
50 M	Movicol (3350)	Generalised urticaria, profound hypotension and LOC (acute tryptase 57 ng/ml)	Chronic fatigue syndrome Depression and anxiety	Sertraline (PEG 400, PS80 in tablet coating) Amitriptyline (PEG MW not known in coating)	SPT Movicol (7/25mm) (2013)	Pos (5/0mm)	Neg	Yes (2 doses)
25 M	Gaviscon Double Action (20,000)	Rhino-conjunctivitis, generalised urticaria, wheezing, cardiac arrest	Ulcerative colitis	Mesalazine (PEG 6000) Pentasa suppositories (PEG 6000) Omeprazole gastro resistant (PEG 6000, PS80) Not specified if tablet core/coating in any of these medications	SPT PEG 20,000 (1%) (2017)	Neg	Neg	Yes (2 doses)
57F	Malarone (PEG 400 & 8000) Methylprednisolone (PEG 3350) Cosmetics	Facial erythema, hand angioedema, SOB Rhinitis, flushing, generalised pruritus, hypotension Conjunctivitis	None	None	SPT Malarone (250mg/ml) 3350 (50%) 4000 (10%) 20,000 (0.001%) (2016)	Pos (7/12mm)	Pos (4/10mm)	Yes (1/5 th dose and after 30m 4/5 th (2 doses)
49F	Gaviscon Double Action (PEG 20,000) Bisacodyl (6000) Cosmetics	Generalised urticaria Cough, SOB, pruritus Pruritus, cough, SOB	TIA	Atorvastatin (PEG 8000 in tablet coating) Clopidogrel (PEG 4000 tablet coating) Fluarix Tetra influenza vaccine (PS80) (2017 ^a)	PEG SPT neg After neg IDTs developed coughing, urticaria and hypotension (2017 ^a)	ND	Neg	Yes (community) (2 doses)
73F	Moviprep (PEG 3350) Penicillin V (PEG 6000) Clopidogrel (PEG 6000) Aspirin (NK)	Pruritus and SOB Generalised pruritus Generalised pruritus Urticaria, SOB, profound hypotension (Acute tryptase 32 ng/ml)	IHD (previous MI) Sigmoid colectomy for dysplastic polypzz	Cetirizine (PEG 400 not specified if tablet core/coating) Adjuvanted Trivalent Influenza Vaccine (PS80)	PEG SPT neg PEG IDT 20,000 (1%) Caused systemic reaction (acute tryptase 36ng/ml) (2017)	ND	Neg	Yes (community) (2 doses)

Abbreviations: AZ, AstraZeneca COVID-19; IDT, intradermal; IHD, ischaemic heart disease; m, minutes; MI, myocardial infarction; MW, molecular weight; ND, not done; Neg, negative; NK, not known; PEG, polyethylene glycol; Pos, positive; PS80, polysorbate 80; RR, respiratory rate; SOB, shortness of breath; SPT, skin prick test; ST, skin tests; TIA, transient ischaemic attack; W/F, weal/flare.

^aThis patient was initially referred in 2013 following a reaction to Gaviscon Double Action; there was over a 2-year delay to obtain the PEG molecular weight from the pharmaceutical company.

been previously reported,^{7,8} but two patients have not been previously reported. Details of the index reactions can be found in Table 1.

Seven of the eight patients received 2 doses of the AstraZeneca COVID-19 vaccine without allergic reaction. Two patients (females) were successfully vaccinated with both doses of the AstraZeneca COVID-19 vaccine in the community before they received our invitation to attend. Both patients tolerated influenza vaccine containing PS80. One patient received and tolerated one full dose of the AstraZeneca COVID-19 vaccine, after experiencing anaphylaxis with the Pfizer/BioNTech COVID-19 vaccine administered as her first COVID-19 vaccine dose.⁷ Two of six patients had positive SPT to PS80. Of these 2 patients, one was taking sertraline (Milpharm LTD, Middlesex, UK) containing PS80 in the coating. One of the 2 patients who had positive SPT to PS80 had a positive SPT to the AstraZeneca COVID-19 vaccine. This was a 55-year-old woman who gave a history of anaphylaxis to Malarone [(PEG 400 and 8000) GlaxoSmithKline, Middlesex, UK] and to IM methylprednisolone acetate (Depo-Medrone, PEG 3350) (Pfizer). PEG skin tests confirmed allergy 5 years ago, and she had not had any further reactions since diagnosis. She was the only patient to receive the first AstraZeneca COVID-19 vaccine in divided doses because of the positive SPT to PS80 and AstraZeneca.

4 | DISCUSSION

PEG is a polymer of ethylene oxide. PS80 is also a polymer of ethylene oxide but is derived from polyethoxylated sorbitan and oleic acid explaining the skin-test cross-reactivity between PEG and polysorbate (Figure 1). This is of particular importance for PEG-allergic patients who are unable to have mRNA COVID-19 vaccines as they contain PEG 2000 but are currently also deprived of alternative COVID-19 vaccines containing PS80. Currently, there are no available COVID-19 vaccines in the UK, which do not contain either PEG

or PS80, and therefore, these unvaccinated patients remain at risk of infection from COVID-19.

Of the eight patients with allergy to PEG, seven of the eight patients were confirmed to have PEG allergy with positive SPT to PEG. One patient did not have skin tests to PEGs, as he was the first patient seen in 2013 when PEG skin-test solutions were unavailable, but diagnosis was confirmed with a positive SPT to undiluted Movicol containing PEG 3350 (Norgine, Middlesex, UK). As in other reports of PEG allergy, all patients were referred to our allergy clinic following anaphylaxis to a PEG-containing drug.¹⁰ However, four of the eight PEG-allergic patients were taking and tolerating some drugs that contained PEG. We had previously reported that the threshold for each subject depended on a combination of molecular weight and amount of PEG in the drug, which is mostly unknown and not disclosed on the summaries of product characteristics by the pharmaceutical industry. Although this supports our previous hypothesis of a threshold effect for PEG allergy, there are also likely to be additional factors in play. For example, lower molecular weights are less allergenic. Skin tests to lower molecular weight are less likely to give a positive skin-test result and however may come up positive to higher molecular weights.¹¹ In addition, the proportion of PEG absorbed by the GI tract decreases with higher molecular weights. It is likely that specific IgE to PEG wanes the longer the patient avoids PEG.¹² Tolerance induction is also possible by taking small amounts of PEG in daily medications. It is noteworthy that the patient whose severe allergic reaction resulted from PEG 20,000 tolerates drugs containing PEGs of lower molecular weight (6,000). Therefore, higher molecular weights taken orally are allergenic only if consumed above a threshold quantity due to reduced absorption. Lower molecular weights have greater GI absorption, and therefore inherently less allergenic may result in allergic reactions at lower concentrations. PEG allergy is rare, and there is little in the literature about it; however, we have a large cohort of 8 patients, and in our experience, individual responses are further modified by the length of time since last exposure and tolerance-induction by taking

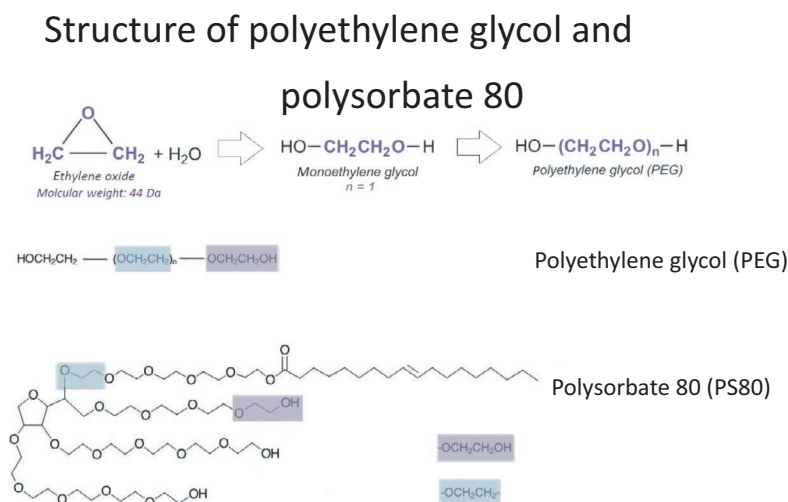
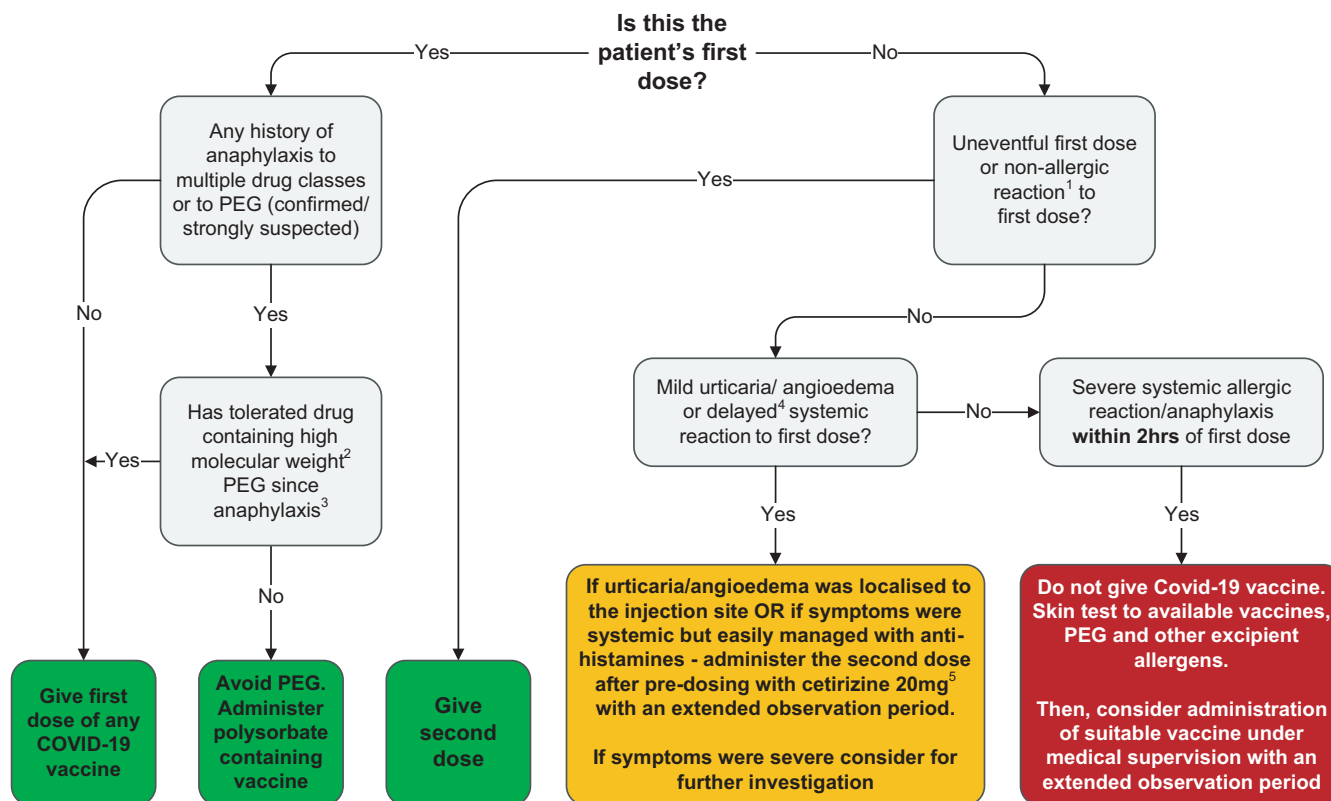


FIGURE 1 Structure of polyethylene glycol and polysorbate 80

Algorithm for allergy specialists for patients with a history of anaphylaxis prior to COVID-19 vaccination



1. Vasovagal episodes, non-urticarial skin reaction or non-specific symptoms. 2. Molecular weight ≥ 2000 3. Refer to SPC section 6.1 for excipient contents of current or recent drugs. 4. Delayed is >2 hrs post-dose. 5. Continue with cetirizine 10mg bd for 3-5 days if symptoms lasted >24 h. PEG – Polyethylene glycol

FIGURE 2 Algorithm for allergy specialists for patients with a history of anaphylaxis prior to COVID-19 vaccination

a PEG-containing drug regularly. Despite individual variances in threshold, these patients remain at risk of anaphylaxis and therefore should carry adrenaline auto-injectors, as PEG is not easily avoidable and amounts and molecular weights not easily identifiable.

Stone described 2 patients who had anaphylaxis to PEG 3350 with positive skin tests to PS80.⁹ Neither of these patients had experienced an allergic reaction to a product containing PS80 despite their positive skin-test result. Patient 1 had positive SPT to PEG 3350, methyl prednisolone acetate (PEG 3350), triamcinolone acetonide (PS80) and PS80 eye drops and conjugated pneumococcal vaccine (PS80). Patient 2 had a positive intradermal to triamcinolone acetonide (PS80), but negative skin tests to PEG although had a subsequent positive challenge to PEG 3350. However, a recent study has shown the irritant effect of the PS80 containing refresh tears.¹³ In addition, 3 patients in this study had positive intradermals to methylprednisolone (PEG 3350) and tolerated the second mRNA COVID-19 vaccine.

In our study, all 8 patients tolerated the AstraZeneca COVID-19 and 7/8 patients tolerated two doses of the vaccine. Two of the six patients had a positive SPT to PS80, and one had previous anaphylaxis to Depo-Provera containing PEG and PS80. Thus, 4 of 6 PEG-allergic patients had negative skin tests to PS80. Therefore, results from this study suggest that PEG-allergic patients can be safely

vaccinated with the AstraZeneca COVID-19 vaccine even if they have positive skin tests to PS80. We cannot, however, confirm the safety of all PS80 vaccines in patients with PEG allergy as it should be noted that the AstraZeneca COVID-19 vaccine contains <100 micrograms of PS80,⁴ which is likely to be a smaller quantity than most other non-COVID vaccines containing PS80 as an excipient. Janssen/Johnson and Johnson COVID-19 vaccine contains 0.16 mg of polysorbate 80.¹⁴

We propose an algorithm for the management of patients with a history of anaphylaxis prior to COVID-19 vaccination (Figure 2). This includes the management of those identified as possible PEG allergic, and those who have had reactions to the first dose of the COVID-19 vaccine. Cutaneous reactions are common following COVID-19 vaccination,¹⁵ and we propose premedication with anti-histamines before the second dose.

In conclusion, we have demonstrated that PEG-allergic patients may safely receive the AstraZeneca COVID-19 vaccine. Patients suspected to have allergy to PEG can also be vaccinated with the AstraZeneca COVID-19 vaccine whilst waiting for allergy investigation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Priya Sellaturay involved in conceptualization, project administration, resources, investigation, data collection, writing original draft, review and editing. Padmalal Gurugama, Verah Harper involved in data collection, resources, review and editing. Tom Dymond created algorithm and amended the version following review. Pamela Ewan involved in resources, contributed to parts of text, key messages, review and editing. Shuaib Nasser involved in data collection, investigation, contributed to parts of text, resources, review and editing. All are accountable and gave final manuscript approval.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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