

BRIEF COMMUNICATION

Patients with previous immediate hypersensitivity reactions to polyethylene glycol can safely receive the BNT162b2 mRNA COVID-19 vaccine

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Abstract

Previous anaphylaxis or immediate allergic reaction to polyethylene glycol (PEG; also known as macrogol) is considered a contraindication to the BNT162b2 mRNA COVID-19 vaccine, which contains 50 ug of PEG at a molecular weight of 2000, and this component is thought to account for the higher rate of anaphylaxis seen with this vaccine (4.7 per million doses) than with other non-mRNA vaccines. However, there is evidence that both anaphylaxis to PEG and anaphylaxis to the Pfizer COVID-19 reaction may not be IgE-mediated, with patients with anaphylaxis to first dose of the Pfizer COVID-19 vaccine receiving their second dose of vaccine without no or milder reactions in a high-risk clinic setting. In New Zealand, non-PEG-containing COVID-19 vaccines were not available until late 2021. Therefore, we offered patients with known or suspected PEG anaphylaxis their first dose of Pfizer COVID-19 vaccine in a high-risk hospital clinic. Eleven patients with previous hypersensitivity to PEG (including eight with anaphylaxis) successfully received their first dose with mild or no reactions; all have now had their second doses in the community without significant reaction. Record review also showed that most patients with previous hypersensitivity reactions to pegylated asparaginase have also been successfully vaccinated. This demonstrates that previous PEG hypersensitivity, including anaphylaxis, does not exclude immunisation with the Pfizer COVID-19 vaccine.

Previous anaphylaxis or immediate allergic reaction to polyethylene glycol (PEG; also known as macrogol) is stated as a contraindication to the BNT162b2 mRNA COVID-19 vaccine, which contains 50 ug of PEG at a molecular weight (MW) of 2000 in the form 2 [polyethylene glycol]-2000]-N, N-ditetradecylacetamide.¹ PEG is commonly found in medications, personal care products and even foods; however, allergy is rare and appears to relate not just to the presence of PEG but to the MW.² Most reported cases of PEG anaphylaxis are to PEG3350 or higher.

Skin prick and intradermal testing (SPT/ID) to PEG3350 confirm the role of IgE in many of these reactions.³ Enzyme-linked immunoassay and basophil activation testing have also been used in diagnosis.

However, results for other MW PEG are less reliable, and PEG-specific IgG antibodies have also been demonstrated. These can cause complement-activated pseudoallergy, which may be responsible for reactions to PEGylated medications.²

The mRNA COVID-19 vaccines are the first vaccines to contain PEG. Anaphylaxis to BNT162b2 occurs at a rate of 4.7 per million doses, higher than that seen with other vaccines.⁴ Suspicion has fallen on PEG2000 as the most likely cause. Small numbers of patients with anaphylaxis to the first dose of BNT162b2 have been revaccinated without experiencing further significant reactions.⁵ This suggests that such reactions might not be IgE mediated.

In Aotearoa New Zealand BNT162b2 was provisionally approved 3 February 2021 and subsequently rolled out across the country. Although the regulatory body

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Table 1 Patients with previous immediate hypersensitivity reactions to polyethylene glycol who attended a hospital-based high-risk clinic for first dose of BNT162b2 mRNA COVID-19 vaccine

Age (year)	Sex	Ethnicity	Indication	Investigations/challenge	Reaction to first dose	Second dose tolerated
Reactions to bowel preparation containing PEG (macrogol) 3350						
52	F	NZ Euro	Anaphylaxis to Glycoprep-C Brighton Level 1	SPT to 1% Glycoprep negative SPT to 1% Picosalax negative Tolerated Picosalax	None	✓
66	M	NZ Euro	Anaphylaxis to Glycoprep-C Brighton Level 1	SPT to 1% PS80 positive SPT to 1% PEG300 [†] negative Tolerated Picoprep	None	✓
31 [†]	M	NZ Euro	Anaphylaxis to Glycoprep Brighton Level 1	Unable to test due to dermatographism	None	✓
58	M	NZ Euro	Anaphylaxis to Klean-Prep Brighton Level 1	None	None	✓
32	M	NZ Euro	Anaphylaxis to MoviPrep Brighton Level 3	None	Transient right sided chest pain ~20 min after vaccine	✓
54	F	NZ Euro	Urticaria, nausea and vomiting with MoviCol	None	Urticaria ~2 h post vaccine	✓
68	F	NZ Euro	Urticaria with Glycoprep	None	None	✓
60 [‡]	F	NZ Euro	Urticaria with MoviCol	None	Nausea	✓
Reactions to other pegylated medications						
16	F	Chinese	Anaphylaxis to pegasparaginase Brighton Level 1	Tolerated erwinase	None	✓
26	M	NZ Euro	Anaphylaxis to pegasparaginase Brighton Level 1	None	None	✓
58	F	NZ Euro	Anaphylaxis to pegfilgrastim Brighton Level 1	Tolerated unpegylated filgrastim	None	✓

[†]Received split doses of vaccine 10%/90% at 15 min interval due to concern by the patient's physician.

[‡]PEG3350 not available at initial appointment and patient did not attend their scheduled follow up.

Medsafe has also provisionally approved the ChAdOx1 nCoV-19, NVX-CoV2373 and Ad26.COV2.S COVID-19 vaccines, all of which do not contain PEG. ChAdOx1 nCoV-19 only became available from 29 November 2021 and NVX-CoV2373 from 10 March 2022. Prior to this, we were unable to offer patients with previous PEG anaphylaxis any alternative.

Patients with presumed PEG hypersensitivity were referred to our department from practitioners in the upper half of the North Island. Given the literature supporting the hypothesis that reactions to both PEG and the vaccine might not be IgE-mediated and could be reduced or prevented with pre-medication, as well as increasing spread of COVID-19 within the community, after initial assessment to determine suitability, we offered them a first dose of BNT162b2 in a hospital-based high-risk clinic. This clinic also administers second doses to those with anaphylaxis to their first dose. Those who chose to attend provided written and verbal consent to vaccination.

We did not perform SPT/ID prior to vaccination, although some patients had SPT done previously. SPT/ID to PEG (as macrogol 3350 or PEG300) is only available

by special arrangement, and was not available at all during the time period of this study due to COVID-19 restrictions. The utility of skin testing in general in predicting reactions to COVID vaccination is also uncertain.⁶ Basophil activation testing is not available in Aotearoa New Zealand. Instead, all relevant clinical records were reviewed by at least two clinical immunologists to confirm likely PEG-induced hypersensitivity.

All patients received oral cetirizine or loratadine 20 mg at least 30 min before vaccination. Two patients received BNT162b2 as a split dose (10%/90% at 15 min) due to concern by their attending physician; all other patients received a single standard dose. Adrenaline, oxygen, and intravenous fluids were all readily available. Patients were observed for 30–120 min after vaccination. Results are shown in Table 1.

Eleven patients attended the high-risk clinic for PEG hypersensitivity (Table 1). Five patients had a history of anaphylaxis to PEG3350 in bowel preparations; four with Brighton level 1 anaphylaxis had symptoms within 30 min of exposure, the fifth had Brighton level 3 anaphylaxis at 1 h. Two of these had previously had SPT

done to PEG +/- polysorbate 80 (although results were largely unhelpful; none had intradermal testing) and had tolerated non-PEG bowel preparation, one was unable to be tested due to dermatographism, and two had not previously been assessed by the immunology department. Three patients reported urticaria with PEG3350 in bowel preparations, none of whom had been previously assessed. Three patients had anaphylaxis to pegylated medications and two of these had subsequently tolerated unpegylated related/identical medications.

None of the patients had anaphylaxis to the vaccine. Three had minor symptoms (chest pain, nausea, delayed urticaria) that settled without treatment. All of these patients have now had their second vaccine dose in the community without reaction.

Following our experience with successfully vaccinating patients with previous pegasparaginase anaphylaxis, we reviewed local paediatric oncology records and found that of the 38 patients recorded as having hypersensitivity reactions to pegasparaginase who were now eligible for the vaccine (≥ 12 years), 27 had received at least one dose with no reaction and 20 are now fully vaccinated. This is consistent with the experience of the Hospital for Sick Children in Toronto and suggests that this reaction may be due to asparaginase rather than PEG.⁷ Subsequent to this we have recommended all these patients receive their vaccines in the community.

These findings support that BNT162b2 can be given safely to patients with presumed PEG hypersensitivity reactions.

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