Patients with polyethylene glycol allergy can experience immediate-type hypersensitivity reactions after exposure to analog substances

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Accepted 23 July 2023

SUMMARY

Polyethylene glycol (PEG) allergy has been recently observed after COVID-19 mRNA vaccination. We present a case of a patient with a history of two hospitalisations for unexplained recurrence of immediate-type hypersensitivity reactions and anaphylaxis who was diagnosed with PEG allergy in early childhood. Subsequently, he was instructed to avoid using PEG-containing daily necessities and drugs. However, in middle childhood, he presented with immediate-type hypersensitivity reactions after taking PEG-free antibiotics. The prick test was positive for the whole drug but negative for its active ingredient. PEG can cross-react with compounds with a C–C–O skeleton as analogue substances; accordingly, the presence of a substance with a similar skeleton in the additive may have been the causative factor. Our findings indicate that patients with PEG allergy may experience immediate-type hypersensitivity reactions to analogue substances.

BACKGROUND

Polyethylene glycol (PEG) is used as an additive for optimising many products and is widely used in pharmaceuticals (eg, binders for tablets, base materials for ointments and creams, bowel cleansers and wound dressings) as well as daily necessities, including cosmetics.[1] PEG may be a hidden allergen; further, failure to correctly diagnose PEG increases the risk of re-exposure, with even death possibly occurring from anaphylaxis.[2] PEG has been recently widely recognised as an excipient of the COVID-19 vaccine; however, it is not widely known that PEG is used in many medicines and daily necessities other than vaccines. Polysorbate (PS) is a typical PEG analogue substance; further, some studies have reported cross-reactivity between PEG and PS.[2–4] However, there have been few reports on other analogue substances.

In this report, we describe the case of middle childhood with PEG allergy who developed immediate-type hypersensitivity reactions after using a PEG-free drug. Accordingly, the hypersensitivity reactions were attributed to PEG analogue substances in the additives. Therefore, there is a need to consider PEG analogue substances contained in drug additives when treating patients with PEG allergy.

CASE PRESENTATION

The patient had a history of atopic dermatitis, bronchial asthma, allergic rhinitis and food allergies. In early childhood, the patient developed

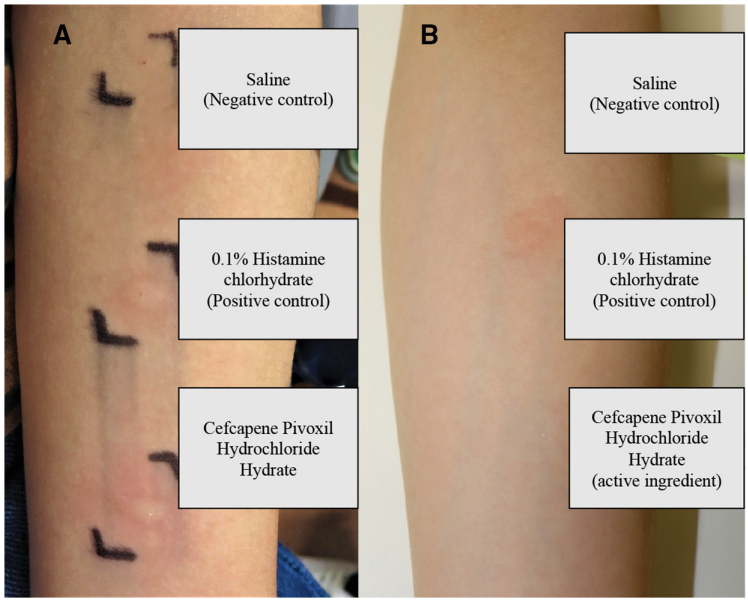

Figure 1 (A) Positive skin prick test for cefcapene pivoxil hydrochloride hydrate (FLOMOX Fine Granules for Paediatrics). (B) Negative skin prick test for cefcapene pivoxil hydrochloride hydrate (only active ingredient).

To cite: Yoshimoto Y, Tezuka J. *BMJ Case Rep* 2023;**16**:e254040. doi:10.1136/bcr-2022-254040

recurrent idiopathic urticaria. Moreover, urticaria appeared when he used heparinoid lotions (HIRUDOID Lotion 0.3%, BESOFTEN Lotion 0.3%). Additionally, he developed anaphylaxis requiring hospitalisation after oral administration of olopatadine hydrochloride (ALLELOCK Granules 0.1%) and an oral spray of xylocaine pump spray (8%). He was admitted to our hospital for investigation of the case. A prick test for ALLELOCK Granules 0.1% was positive. A prick test for the active ingredients and additives of ALLELOCK Granules 0.1% was positive for PEG. Since PEG was similarly present in drugs that had previously caused symptoms, he was diagnosed with PEG allergy. PEG allergy is considered percutaneous sensitisation; additionally, in our case, our patient showed sensitisation caused by the use of PEG-containing sunscreen cream during summer in toddler.[5] After the diagnosis of PEG allergy, instructions were given to just use PEG-free products. For drugs that were likely to be used, a table of PEG-containing and PEG-free formulations was prepared with reference to package inserts. Subsequently, localised urticaria was observed after a PEG-containing topical drug was mistakenly used; however, there were no systemic immediate-type hypersensitivity reactions.

In middle childhood, he was prescribed cefcapene pivoxil hydrochloride hydrate (CFPN-PI; FLOMOX Fine Granules for Paediatric) by a local doctor for balanitis of the glans. Fifteen minutes after taking the drug, he presented with respiratory symptoms (nasal discharge, sneezing and laryngeal discomfort) and skin symptoms (swollen face). After taking antihistamines, he was taken to the emergency room. His vital signs were normal at the time of the visit. Since this was an immediate-type hypersensitivity reaction, his respiratory symptoms disappeared and skin symptoms (puffiness around the eyelids) remained. He was subsequently hospitalised for observation. The skin symptoms improved quickly and he was discharged the next day without the occurrence of biphasic reactions.

OUTCOME AND FOLLOW-UP

A skin prick test was performed for CFPN-PI and its active ingredient, with saline as a negative control and 0.1% histamine chlorhydrate solution as a positive control. It was positive for CFPN-PI and negative for its active ingredients (figure 1). Accordingly, additives containing polyoxyethylene (160) and polyoxypropylene (30) glycol, which are PEG analogue substances, were considered to be the causative agents. After discharge, he was instructed to avoid using drugs and daily necessities containing PEG and its analogues. Moreover, since PEG analogue substances may have induced the immediate-type hypersensitivity reactions, we prescribed an epinephrine auto-injector in case of anaphylaxis and confirmed the response in case of accidental contact. He is yet to present any further systemic immediate-type hypersensitivity reactions.

DISCUSSION

In 2018, the first report of immediate-type hypersensitivity reactions to PEG in children was a case of accidental ingestion of an alkaline battery and the use of a bowel cleanser.[6] PEG allergy may be misdiagnosed as idiopathic allergy or chronic urticaria; further, it should be considered in patients with recurrent symptoms resulting from seemingly unrelated products.[1] PEG has become recently widely recognised as the causative antigen for allergic reactions to the COVID-19 mRNA vaccine. Furthermore, PEG-specific IgE and IgG antibodies are associated with immediate-type hypersensitivity reactions.[4]

PS is also widely used in daily necessities, including foods, cosmetics, excipients for pharmaceuticals and vaccines. PS is considered a PEG analogue substance since it shares a common chemical moiety with PEG; moreover, there is cross-reactivity between PEG and PS.[2–4] Therefore, it is important to consider that PS may induce immediate-type hypersensitivity reactions in patients with PEG allergy.

PEG has exhibited cross-reactivity with other polymers containing C–C–O skeletons, which are structurally similar to PEG. This could be attributed to anti-PEG antibodies reacting against polymers with a C–C–O skeleton.[7] In our case, the additive contained polyoxyethylene (160) polyoxypropylene (30) glycol, which has a C–O–O skeleton and could have been the causative agent.

Although there has been increasing awareness of PEG allergy with the widespread use of COVID-19 mRNA vaccines, it remains insufficiently recognised that PEG is contained in numerous daily necessities and medicines other than vaccines. Further, there is insufficient awareness that even analogue substances may cause immediate-type hypersensitivity reactions. Further, in patients with PEG allergy, it is important to be aware that not only PEG but also analogue substances can cause immediate-type hypersensitivity reactions.

Patient's perspective

Until I was diagnosed with PEG allergy in early childhood, I had repeated episodes of urticaria and anaphylaxis with unclear causes, which made me very anxious. After the diagnosis, the anxiety was alleviated since I understood the cause, which improved the quality of my daily life.

However, this time, the symptoms appeared after taking something without PEG, which made me fear that I would return to my previous anxious life. However, thanks to the thorough investigation of the cause, I was made aware that symptoms could occur even with PEG analogues, which laid my fears to rest. (Translated from Japanese)

Learning points

- To diagnose a polyethylene glycol (PEG) allergy, it is important to include a differential diagnosis in patients who present with recurrent symptoms resulting from seemingly unrelated products.
- In patients with PEG allergy, even PEG analogue substances can induce immediate-type hypersensitivity reactions; therefore, they should be carefully considered.
- It is difficult to completely avoid PEG and PEG analogue substances in daily life. Therefore, patients with PEG allergy should carry an epinephrine auto-injector given the risks of re-exposure and anaphylaxis.

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Acknowledgements We would like to thank Editage (www.editage.com) for English language editing.

Contributors YY and JT were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms, and critical revision for important intellectual content. YY and JT gave final approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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