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Case report

## Positive skin test to pegylated drug in a patient with anaphylaxis to polyethylene glycol

*Prick-test positif pour les médicaments pégylés chez un patient aux antécédents d'anaphylaxie au polyéthylène glycol*

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### Abstract

We report a case of a woman who presented anaphylaxis to polyethylene glycol (PEG) associated with positive skin tests to a pegylated drug. To the best of our knowledge, this is **the first case**, which suggests a **potential allergy to pegylated drugs in patients with anaphylaxis to PEG**. With the increasing use of pegylated drugs, physicians and patients should be informed of this potential allergy because drug databases do not always clearly indicate that pegylated drugs contain PEG.

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**Keywords:** Polyethylene glycol; Pegylated drugs; Adverse drugs reaction; Cross-reactivity

### Résumé

Nous rapportons le cas d'une femme ayant présenté un choc anaphylactique au polyéthylène glycol (PEG) associé à des prick-tests positifs pour un médicament pégylé. À notre connaissance, il s'agit de la première observation qui suggère une potentielle allergie aux médicaments pégylés chez une patiente présentant une anaphylaxie au PEG. Devant l'utilisation croissante des médicaments pégylés, les médecins et les patients devraient être informés des risques encourus en cas d'allergie au PEG, d'autant que les bases de données ne mentionnent pas toujours clairement les médicaments qui contiennent du PEG, y compris les médicaments pégylés.

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**Mots clés :** Polyéthylène glycol ; Médicaments pégylés ; Effets indésirables des médicaments ; Réaction croisée

Polyethylene glycol (PEG) is commonly used as a laxative. **Anaphylactic reaction to laxative or cosmetic drugs containing PEG is well-documented in the literature [1–4].** In recent years, PEG has also been attached to other molecules to increase their half-life. These molecules are commonly known as pegylated drugs (Table 1). To date, cross-reactivity between PEG and pegylated drugs is unknown. We report the case of a patient who presented with anaphylactic shock caused by PEG and a

positive skin prick-test result for a pegylated drug (pegylated interferon- $\alpha$ 2a [IFN- $\alpha$ 2a]).

### 1. Observation

A 57-year-old woman was prescribed ketoprofen, tramadol and esomeprazole by her general practitioner for mechanical left shoulder pain. Analgesic treatment was complicated by constipation and the patient was prescribed PEG (also named macrogol). Ten minutes after the first oral intake of PEG, pruritus developed on the palms of her hands. A few minutes later, she became weak and dizzy and generalized urticaria

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Table 1  
The main approved pegylated drugs.

Pegylated drugs	Indications
Pegademase bovine (Adagen <sup>®</sup> ) (Adenosine deaminase)	Severe combined immunodeficiency disease associated with adenosine deaminase deficiency
Pegaspargase (Oncaspar <sup>®</sup> ) (Asparaginase)	Acute lymphoblastic leukemia
Interferon- $\alpha$ 2b (PegIntron <sup>®</sup> )	Chronic hepatitis C
Interferon- $\alpha$ 2a (Pegasys <sup>®</sup> )	Chronic hepatitis C or B
Pegvisomant (Somavert <sup>®</sup> ) (Human growth hormone mutein)	Acromegaly
Methoxy PEGepoietin-beta (Mircera <sup>®</sup> )	Chronic renal failure anemia
Pegfilgrastim (Neulasta <sup>®</sup> )	Post-chemotherapy neutropenia
Certolizumab (Cimzia <sup>®</sup> )	Rheumatoid arthritis

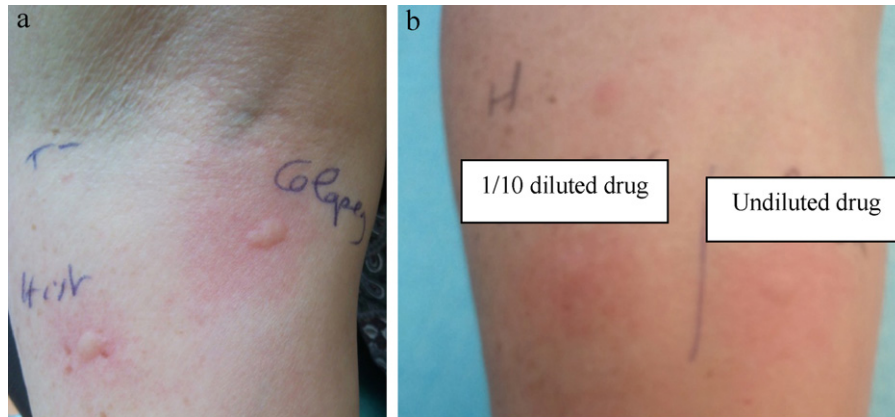


Fig. 1. a: skin prick-test with histamine and polyethylene glycol (Colopeg<sup>®</sup>). The test was positive for polyethylene glycol; b: skin prick-test with pegylated interferon: erythema with diluted solution (1/10), and papule with undiluted solution.

appeared. When the medical team arrived, the patient's blood pressure was low (systolic pressure 60 mmHg). She was given an intramuscular injection of epinephrine (0.5 mg) associated with prednisone (60 mg). The patient responded rapidly to the treatment and was discharged after 24 hours observation in intensive care.

Six weeks after this reaction, the patient was given skin prick-tests for PEG (Colopeg<sup>®</sup>). These tests were positive to undiluted PEG (Fig. 1a). A challenge test was also performed to rule out intolerance to non-steroidal anti-inflammatory drugs (NSAID). This test was negative with nimesulide. The patient regularly self-administered oral suspension of esomeprazole or tramadol with no adverse effects, so the reaction could not be imputed to these drugs. These results strongly suggest an anaphylactic reaction to PEG. With the increasing use of pegylated drugs for various indications, the risk of the patient receiving one of these drugs in the future is high. **We, therefore, tested the patient's skin reactivity to pegylated drugs in order to warn her of this potential reaction. Skin prick-test to pegylated IFN- $\alpha$ 2a was positive for the undiluted drug (Fig. 1b), whereas erythema without papules was observed with a 1/10 dilution. We advised the patient to avoid cosmetics and drugs containing PEG, including pegylated drugs.**

## 2. Discussion

PEG is a polymer of ethylene oxide (HO—CH<sub>2</sub>—(CH<sub>2</sub>—O—CH<sub>2</sub>)<sub>n</sub>—CH<sub>2</sub>—OH), available in high- or low-molecular

weight forms. The high-molecular weight form is used in particular as an osmotic laxative [5]. Anaphylactic reaction to this form of PEG (around 4 kDa) is rare but well-documented in the literature [1–4]. For over a decade, PEG has also been conjugated to some drugs to improve their half-life (Table 1). For example, pegylated IFN- $\alpha$ 2a is indicated to treat chronic hepatitis C as it allows dose frequency to be reduced. **Anaphylaxis is an adverse event that can be caused by pegylated drugs, but no details are available.** To the best of our knowledge, this is the first case in which an anaphylactic reaction to PEG has been associated with positive skin tests for a pegylated drug (pegylated IFN- $\alpha$ 2a). PEG-IFN- $\alpha$ 2a contains a 40 kDa PEG molecule attached by a covalent bond to the IFN- $\alpha$ 2a core protein [6]. In most cases, PEG is attached to Lys31, Lys121, Lys131 or Lys134 of IFN- $\alpha$ 2a. The covalent bond between PEG and interferon, used to produce pegylated drugs, does not seem to decrease PEG allergenicity. Other pegylated molecules, such as pegfilgrastim (pegylated G-CSF) and pegylated epoietin-alpha (pegylated erythropoietin), were not tested, but pegfilgrastim and pegylated epoietin alpha also contain a methoxypolyethylene glycol molecule with a high molecular weight (around 20 kDa).

## 3. Conclusion

Anaphylaxis caused by PEG can be associated with positive skin prick-tests for pegylated drugs. Physicians and patients should, therefore, be informed of this potential allergy because

drug databases do not always clearly indicate that pegylated drugs contain PEG.

Novel insight:

- patients with anaphylaxis to PEG might present allergy with pegylated drugs;
- this potential allergy should be known by physicians because drug databases do not always clearly indicate that pegylated drugs contain PEG.

#### **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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