Recurrent Immediate Type Hypersensitivity Reaction Induced by Macrogol in a 3-Year-Old Boy

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J Investig Allergol Clin Immunol 2020; Vol. 30(1): 72-73
doi: 10.18176/jiaci.0447

Key words: Macrogol. Polyethylene glycol. Immediate hypersensitivity reaction. Sensitization. Children.

Palabras clave: Macrogol. Polietilenglicol. Reacción de hipersensibilidad inmediata. Sensibilización. Niños.

Macrogol (polyethylene glycol [PEG]) is a polyether compound that is widely used as an additive in pharmaceuticals, cosmetics, and food because of its stabilizing properties [1]. Immediate-type hypersensitivity to macrogol has been reported in adults after intake of the drug in tablet form [2], injection of corticosteroid solutions [3], and ingestion of bowel-cleansing preparations [4]. However, to our knowledge, only 1 pediatric case has been reported to date [5]. We report a case of recurrent hypersensitivity reactions induced by macrogol in a 3-year-old boy. Our findings emphasize the need for increased awareness of hypersensitivity to additives in children. The parents gave their written informed consent for the publication of this report.

The patient was a 3-year-old boy with a previous history of atopic dermatitis, bronchial asthma, allergic rhinitis, and food allergy. He was born at term via vaginal delivery and was breastfed from birth. At 3 months of age, he was diagnosed with atopic dermatitis and treated with moisturizer and topical corticosteroids. At 3 years of age, a few minutes after administration of olopatadine hydrochloride (ALLELOCK Granules 0.1%), he experienced an unusual sensation in the pharynx, followed by urticaria and cough 10 minutes later. Generalized urticaria developed, and coughing became exacerbated. These symptoms improved in 3 hours without medical treatment. Two months later, the patient was treated for cavities after induction of anesthesia via xylocaine pump spray 8% at a dental office. He vomited 30 minutes after the end of treatment and rapidly developed generalized urticaria and repetitive vomiting, which required medical treatment in the emergency department. He recovered in the emergency department after oral administration of loratadine (Claritin Dry Syrup 1%). Subsequently, he sometimes developed urticaria when he applied diphenhydramine hydrochloride cream (Restamin KOWA Cream 1%), lidocaine cream (EMLA Cream 5%), or heparinoid lotion (HIRUDOID Lotion 0.3% or BESOFTEN Lotion 0.3%). Although he was required to continue dental treatment, the cause of the allergic symptoms was unclear. He came to our hospital for diagnosis of the cause of these recurrent hypersensitivity reactions. Causal relationships were established between the onset of symptoms and the use of ALLELOCK Granules 0.1% and Restamin KOWA Cream 1%. Furthermore, the patient had previously undergone a skin prick test (SPT) with these drugs at another hospital. As the SPT yielded a positive result, we performed an open patch test with the basic ingredients and additives of both drugs, which were provided by the manufacturers. A wheal with itching appeared 10 minutes after application of macrogol to the skin; the result was classed as positive. We considered macrogol to be the cause of his hypersensitivity reaction and examined the relationship between clinical symptoms and the presence or absence of macrogol in the drugs

Table. Polyethylene Glycol (PEG) Contained in Each Drug Used and Its Molecular Weight, Route of Exposure, and Type of Immediate Reactions

Drug	PEG	Molecular Weight, Da	Exposure	Immediate-Type Reaction
ALLELOCK Granules 0.1%	Macrogol	4000	Systemic administration	Oral discomfort, generalized urticaria, cough
Xylocaine Pump Spray 8%	Macrogol	400	Oral spray	generalized urticaria, repetitive vomiting
Restamin KOWA Cream 1%	Polyethylene glycol stearate	2200	Topical medication	Urticaria
EMLA Cream 5%	Polyoxyethylene hydrogenated castor oil	>10000	Topical medication	Urticaria
HIRUDOID Lotion 0.3%	Cetomacrogol	1000	Topical medication	Urticaria
BESOFTEN Lotion 0.3%	Polyoxyethylene polyoxypropylene glycol	8350	Topical medication	Urticaria
CLARITIN Dry Syrup 1%[a]	None	–	Systemic administration	No symptoms

[a]CLARITIN Dry Syrup did not generate an immediate reaction.

used (Table). All drugs with which hypersensitivity reactions occurred were found to contain macrogol. Conversely, Claritin Dry Syrup did not contain macrogol. Given the differences in molecular weight of macrogol between the drugs (Table), we performed SPTs using various molecular weights (macrogol 100, 200, 1500, 4000, 6000, and 20 000). The SPT results were positive to macrogol 4000 (Nikko) (200 mg/mL), macrogol 6000 (Nikko) (200 mg/mL), and macrogol 20 000 (Nikko) (200 mg/mL). The SPT results were negative to macrogol 100 (Nikko) (200 µL/mL), macrogol 200 (Nikko) (200 µL/mL), and macrogol 1500 (Nikko) (200 mg/mL). Delayed readings of each macrogol after 24 hours were negative. Based on these results and the previous history, the patient was diagnosed with immediate hypersensitivity reaction to macrogol. We did not have the equipment available to perform the lymphocyte stimulation test, basophil activation test, or dot blot assay. We planned to perform an SPT for Xylocaine Pump Spray 8%, which contained macrogol 400, although could not because the patient's parents refused skin tests for the drug. Additionally, the patient's parents refused an oral challenge with macrogol. After discharge, drugs and toiletries containing macrogol were avoided; no subsequent hypersensitivity reactions were observed, except when the patient used Atolant Cream 1%, which contained cetomacrogol (polyoxyethylene cetyl ether).

Macrogol is widely used in toiletries (eg, lipsticks, toothpaste, and cosmetics) and medicines (eg, oral drugs, suppositories, intravenous injection, and external medications). Although macrogol is generally considered biologically inert, the incidence of hypersensitivity to this agent has recently increased in adults [1]. Furthermore, a case of IgE-mediated anaphylaxis induced by macrogol has been reported [6]. However, awareness of the allergic potential of macrogol remains poor among medical professionals [1], of whom very few suspect macrogol as the causative agent in immediate hypersensitivity reactions, particularly in children. This is the first report of a case of recurrent immediate-type hypersensitivity reaction induced by macrogol in a child.

A previous report described repeated cutaneous exposures to macrogol before the onset of systemic reactions to medications containing macrogol [7], suggesting percutaneous sensitization to the drug. Sensitization in this case may have been induced by a sunscreen cream containing macrogol, which was used for 4 months in the summer when the patient was 1 year of age. We did not perform an open patch test for the sunscreen cream, because the patient's parents refused. Although high-molecular-weight macrogol (>500 g/mol) is generally considered unable to penetrate normal skin and mucosa [8], the literature contains reports of increased penetration of macrogol in the skin of patients with atopic dermatitis [9]. We presume that various molecular-weight macrogols (eg, polyoxyethylene glyceryl isostearate [3000 Da], lauryl PEG-9 polydimethylsiloxyethyl dimethicone [450 Da], PEG-10 dimethicone [500 Da], and polysorbate 60 [3000 Da]) included in the sunscreen cream might have penetrated the patient's atopic skin because of a defective barrier function, thereby establishing sensitization. In recent years, owing to percutaneous sensitization, skin care and moisturizing agents have been increasingly used to prevent the onset of food allergies in children [10]. Although it is good for infants to use skin care and moisturizing agents, medical professionals should be aware that infants can become sensitized to additives when the skin lacks proper barrier function. Medical professionals should pay special attention to the allergic potential of these additives in order to prevent patients from experiencing recurrent severe hypersensitivity reactions.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received May 23, 2019; accepted for publication September 3, 2019.

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