An 8-Year-Old Girl with Drug Hypersensitivity to First Triptorelin Acetate Administration

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Abstract
Triptorelin is a synthetic gonadotropin-releasing hormone agonist for the treatment of precocious puberty in children. Among the triptorelin side effects, drug hypersensitivity reactions, including anaphylaxis, can rarely occur, mostly after repeated exposure to the drug. We present a first case of an 8-year-old girl with central precocious puberty who developed anaphylaxis to the first injection of decapetyl depot, which contains triptorelin acetate (D,L lactide coglycolide), dextran 70, and polysorbate 80. She showed 2 positive reactions in an intradermal test to decapetyl depot, suggesting that it is an IgE-mediated reaction to one of its components. Considering this was the first exposure to triptorelin, it might be a reaction to polysorbate. As there are many therapeutic products containing polysorbate which can cross-react with polyethylene glycols, physicians should pay attention to immediate reactions to drugs containing polysorbate.

Keywords
Precocious puberty
Polysorbates
Triptorelin acetate
Anaphylaxis

1. Introduction
Sexual precocity is an endocrine disorder characterized by the onset of secondary sexual characteristics, such as breast development, dental hair development, and increased growth velocity, typically before the age of 8 years in girls and 9 years in boys [1]. Triptorelin is a synthetic gonadotropin-releasing hormone (GnRH) agonist consisting of 10 peptides and is commonly used as a treatment for sexual precocity because it is expected to inhibit the secretion of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Among the adverse effects of triptorelin, hypersensitivity reactions have been reported with repeated exposure, but no case of anaphylaxis on the first dose has been reported [2-5]. As the prevalence of central hypogonadism has increased significantly in Korean children over the past three years [6], we believe that sufficient attention to the adverse effects of drugs for this condition is necessary, and we report the first case of anaphylaxis caused by the first injection of triptorelin in a patient with central hypogonadism.
2. Case

An 8-year-old girl, diagnosed with central sexual precocity (bone age, 9 years, breast, Tanner stage III), was admitted to the emergency medical center with generalized urticaria and swelling of the face with erythema over the cheeks with swelling around the eyes and mouth (Figure 1). The patient’s symptoms began 20 minutes after the first injection (2.5 mg) of triptorelin acetate (Decapeptyl, Ferring Pharmaceuticals Korea, Korea). An itchy skin rash and hives developed on the face, spreading to both arms and trunk, followed by swelling of the face. She did not complain of shortness of breath, abdominal cramps, or dizziness. No family history of allergies was reported. A past medical history of frequent rhinitis that did not affect daily life was noted.

Physical examination: Height was 130.5 cm (50<sup>th</sup> – 75<sup>th</sup> percentile) and weight was 24.9 kg (50<sup>th</sup> – 75<sup>th</sup> percentile). Her blood pressure was 118/69 mm Hg (90<sup>th</sup> percentile < systolic blood pressure < 95<sup>th</sup> percentile, 50<sup>th</sup> percentile < diastolic blood pressure < 75<sup>th</sup> percentile), respiratory rate 22 breaths/min, heart rate 111 beats/min, oxygen saturation 97%, and temperature 37.2°C. Pitting and rash were observed on the face, arms, and trunk. The level of consciousness based on the pediatric Glasgow Coma Scale was 15. The nasal mucosa was pale and swollen. Wheezing breath sounds were heard in both lungs.

Laboratory findings: Blood work showed white blood cells 9.1×10<sup>3</sup>μL, hemoglobin 14.3 g/dL, platelets 269×10<sup>3</sup>μL, serum eosinophil cationic protein 39.80 μg/L (normal: 0.00–24.00 μg/μL), blood eosinophil fraction 1.4%.

Course and treatment: At the emergency medical center, the patient presented with wheezing breath sounds in both lungs, swelling, and rash on the face, arms, and trunk, consistent with anaphylaxis, and was given an intramuscular injection of epinephrine; the wheezing improved and she was admitted to the hospital for observation. She was discharged the next day with no further symptoms. Skin prick tests and intradermal tests were performed one week after discharge. Skin prick tests for 40 allergens (Bencard Corp., Brentford, UK) showed five levels of positivity to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, and the rest of the allergens were negative in response to histamine (Table 1). In intradermal tests, the reaction to triptorelin acetate was stage 2 on the erythema scale and the allergen swelling ratio to the positive control, histamine, was stage 2. The reaction to leuprorelin acetate was the same as the reaction to the negative control, saline, and was stage 1 on the erythema scale (Table 2, Figure 2). The medication was changed from triptorelin acetate to leuprorelin acetate, and treatment is ongoing with no adverse effects after 1 year of treatment. Informed consent for publication was obtained from the guardian and patient.

3. Goal

The 8-year-old girl, in this case, had Tanner stage III, bone age of 9 years, LH peak of 7.32 mIU/mL, and LH/
FSH peak ratio of 1.36 on GnRH stimulation test, which met the criteria for treatment of sexual precocity. The treatment for central sexual precocity is to desensitize the gonadotroph cells, a mechanism also known as pituitary gonadal suppression. When the hormone is administered, the pituitary gland is continuously stimulated to produce LH and FSH, thereby reducing the production of sex steroid hormones [2]. Triptorelin acetate is a synthetic decapeptide (pGlu-His-Ser-Tyr-D/Trp-Leu-Arg-Pro-Gly-NH2). It is a GnRH agonist and is widely used in the treatment of sexual precocity.

Immediate hypersensitivity reactions to triptorelin have been reported very rarely [2-5]. However, they have all occurred during continuous administration of the drug, and there have been no reports of IgE-mediated hypersensitivity reactions after the first dose. This patient presented with skin and mucosal manifestations of urticaria and angioedema and wheezing, which met the criteria for anaphylaxis and resolved after intramuscular epinephrine. The interpretation of intradermal testing is based on erythema: erythema < 5 mm is stage 0, 11–20 mm is stage 1, and 21–30 mm is stage 2 [7]. The patient’s intradermal test to decapeptide injection was stage 2 with erythema of 30 mm and allergen/histamine ratio <1. This suggests the possibility of specific IgE to a specific component in Decapeptyl Injection. In addition to triptorelin acetate, Decapeptil contains the excipients dextran, a D,L-lactide-co-glycolide copolymer, sodium dihydrogen phosphate, sodium chloride, and polysorbate.

The anaphylaxis that occurred in this patient is thought to be a hypersensitivity reaction to either triptorelin acetate or polysorbate 80 in the excipients. However, it is unlikely to be caused by triptorelin acetate due to previous, hence it is deduced that polysorbate likely caused the hypersensitivity reaction. Polysorbates are known to cause non-immunological anaphylactic reactions [8], and a mechanism of anaphylaxis due to an immune response to polysorbates has recently been reported [9]. Polysorbates are found in a variety of products, including foods such as ice cream, various pharmaceuticals, and cosmetics.

Polyethylene glycols (PEGs) are macrogols commonly used during colonoscopies and to treat constipation and are structurally very similar to polysorbates with common antigenic determinants [10]. PEGs are also surfactants and are common ingredients
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in household hygiene products such as soaps, detergents, and disinfectants, hence many people may be exposed to them\textsuperscript{[10]}. Recently, IgE-mediated reactions have been suggested as a mechanism for hypersensitivity reactions to PEGs and polysorbates using skin tests, oral provocation tests, enzyme-linked immunosorbent assays, and chemiluminescence immunosorbent assays\textsuperscript{[8]}. People who develop anti-PEG antibodies to PEGs may develop cross-reactive IgE-mediated hypersensitivity reactions when exposed to agents containing polysorbates\textsuperscript{[11]}.

In this patient, intradermal testing for polysorbate and PEGs could not be performed because the patient’s circumstances precluded further testing that would have provided a more definitive mechanism; therefore, sensitization to polysorbate is unclear. In addition, the likelihood of PEG sensitization is expected to be low as the patient had no history of colonoscopy and no history of urticaria to common household products containing PEGs such as detergents, soaps, and cosmetics. Polysorbate itself has a histamine-releasing effect, suggesting the possibility of a non-IgE-mediated reaction\textsuperscript{[12]}. However, intradermal testing with undiluted decapeptide was positive in the patient and negative in controls tested intradermally at the same concentration. The patient also had a certain World Health Organisation causality indicator for the drug. Therefore, both non-IgE-mediated and IgE-mediated hypersensitivity reactions should be considered in this patient, although definitive testing was not available\textsuperscript{[13]}. In recent years, widespread exposure to polysorbates and PEGs has become common, and vigilance for IgE-mediated reactions to them is warranted.

This patient had a clear allergic predisposition with strong house dust mite sensitization and allergic rhinitis, so it is certainly possible that she was sensitized to polysorbates or PEGs, but unfortunately, this could not be confirmed. However, this case is significant in that it is the first report of anaphylactic hypersensitivity reactions occurring after the first dose of decapeptide. There have been cases of similar allergic reactions after switching to other GnRH agonists\textsuperscript{[14,15]}, but fortunately, our patient was able to safely take leuprorelin acetate, which does not contain polysorbate, and showed no hypersensitivity reactions.

As formulations containing polysorbates or PEGs are common, we would like to point out that hypersensitivity reactions to agents containing polysorbates or PEGs, including GnRH agonists, may be increased and require careful monitoring when using these agents. In particular, patients with a history of allergic disease should be monitored for severe IgE-mediated hypersensitivity reactions such as anaphylaxis, even at the first dose.

**Disclosure statement**

The authors declare no conflicts of interest.

**References**


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