

Patient report

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Anaphylaxis to gonadorelin acetate in a girl with central precocious puberty

DOI 10.1515/jpem-2015-0183

Received May 2, 2015; accepted June 8, 2015; previously published online July 18, 2015

Abstract: Gonadotropin-releasing hormone analogues are generally regarded as safe drugs. Gonadorelin acetate has been widely used for the diagnosis of central precocious puberty, and life-threatening reactions to gonadorelin acetate are extremely rare. Herein, we described – to the best of our knowledge – the first pediatric case in which severe anaphylaxis was encountered after intravenous gonadorelin acetate administration. An 8-year-old girl who was diagnosed with central precocious puberty was receiving triptorelin acetate treatment uneventfully for 6 months. In order to evaluate the efficacy of the treatment, an LH-RH stimulation test with gonadorelin acetate was planned. Within 3 min after intravenous administration of gonadorelin acetate, she lost consciousness and tonic seizures began in her hands and feet. She was immediately treated with epinephrine, diphenhydramine, and fluids. Her vital signs recovered within 30 min. Based on the results, anaphylaxis should be anticipated and the administration of these drugs should be performed in a setting that is equipped to deal with systemic reactions.

Keywords: anaphylaxis; gonadorelin acetate; precocious puberty.

Introduction

Gonadorelin acetate is generally regarded as a safe drug, and has been widely used to diagnose central precocious puberty and to induce ovulation of women with hypothalamic amenorrhea. Although anaphylactic reactions to GnRH analogues that have been used for treatment, such as triptorelin acetate and leuprolide acetate, have been previously reported, life-threatening reactions to gonadorelin acetate are extremely rare. Herein, we described a pediatric case, in which severe anaphylaxis was encountered after intravenous gonadorelin acetate administration.

Case report

An 8-year-old girl with central precocious puberty was referred to our hospital. We were informed that she was admitted to the pediatric endocrinology department of another medical center due to breast development and increased growth when she was just 7.5 years old. Physical examination had revealed Tanner stage III for breast development and her bone age was 10 years old. Thyroid function tests were normal. Basal luteinizing hormone (LH) level was 0.9 mIU/L (normal < 0.3 mIU/L) and basal estradiol level was 28 pg/mL (normal < 10 pg/mL). The diagnosis was confirmed with a luteinizing hormone releasing hormone (LH-RH) stimulation test with gonadorelin acetate.

The peak level of LH in the LH-RH stimulation test was 17.8 mIU/L (normal < 5 mIU/L). They also detected pubertal sizes of uterus and ovaries by pelvic ultrasound. Magnetic resonance imaging revealed no evidence of a tumoral lesion. Triptorelin acetate treatment was initiated. Later, due to relocation of the patient's family, she was referred to our center. Triptorelin acetate therapy was maintained (3.75 mg/28 days, intramuscular) without any adverse effects. However, her growth rate was still higher than the normal range for her age and sex (5.7 cm/6 months).

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during the treatment. Her bone age was 10 years old at the beginning of treatment, and reached 11 years old after 6 months. Therefore, a LH-RH stimulation test with gonadorelin acetate was planned at the 6th month of treatment in order to evaluate the efficacy of the therapy.

During the first interview with the family in our department, no history of allergy to any medications or food was reported. There was also no information concerning a previous adverse reaction in the discharge report of the patient provided by the previous medical center. Nevertheless, within 3 min after an intravenous bolus administration of 0.1 mg gonadorelin acetate, she lost consciousness and tonic seizures began in her hands and feet. She developed generalized hives along with edema on her tongue, lips, and eyelids. Cyanosis was also present and she had hypotension (60/30 mm Hg). Based on the diagnosis of anaphylaxis due to gonadorelin acetate infusion, she was immediately treated with intramuscular epinephrine (0.01 mg/kg; 1:1000), high flow supplemental oxygen (6–8 L/min), IV diphenhydramine (1 mg/kg), and IV methylprednisolone (1 mg/kg). Her vital signs, including blood pressure and pulse rate, recovered within 30 min. Although the patient recovered successfully within 6 h, she was subsequently hospitalized for monitoring of her vital signs and discharged without any further events.

When her medical history was more deeply investigated, her parents recalled that there were several skin reactions along with pruritus after a previous gonadorelin acetate injection. However, as the parents had underestimated the importance of the lesions, they had not informed the healthcare professionals about the symptoms. It was learned that the previous symptoms had improved without any medication. A skin test with gonadorelin acetate was planned during the follow-up, however, it could not be performed due to the unwillingness of her parents.

Discussion

Precocious puberty can be defined as pubertal development that begins at an age earlier than 8 years old in girls and 9 years old in boys (1); it affects 1 in 5000–10,000 children (2). The LH-RH stimulation test with gonadorelin acetate test is the gold standard for determining the type and for assessing the degree of precocious puberty. In addition to diagnosis, GnRH analogues are also used for initiating treatment and for detecting the efficacy of such treatment.

GnRH analogues are generally regarded as safe drugs. However, adverse effects such as local reactions,

headache, and abdominal discomfort have been reported (3). Life-threatening anaphylactic reactions can also be encountered due to the administration of GnRH analogues. However, allergic reactions are very rare in the medical literature, and our case is the first reported child to have encountered anaphylaxis due to gonadorelin acetate. To the best of our knowledge, there are three previous case reports in the adult population: one with anaphylaxis to gonadorelin acetate and two cases with anaphylaxis after gonadorelin hydrochloride injection. The first patient was a 31-year-old man who was treated for oligospermia. He received 100 mcg gonadorelin acetate for diagnosis and was then treated with gonadorelin at a dose of 50 mcg, given subcutaneously every 129 min with a computerized pump. Nine weeks later, he had transient generalized urticaria and 10 weeks later, there was an anaphylactic reaction after the administration of intravenous gonadorelin for the repeat test. An allergic response did not exist after the initial administration of intravenous gonadorelin acetate nor after subsequent subcutaneous injections (4).

The first patient who had anaphylaxis to gonadorelin hydrochloride was a 28-year-old female patient being treated for infertility (5). Gonadorelin hydrochloride had been administered intravenously thrice during a period of 2 years for ovulation induction without adverse effects. She had no history of atopy. An anaphylactic reaction emerged immediately after the 4th dose of gonadorelin hydrochloride. The other patient was a 26-year-old woman who had primary infertility (6). Gonadorelin hydrochloride was administered intravenously several times with uneventful results. However, she presented with generalized welts and itching associated with chest pain and breathlessness after the last administration. For all these cases, it was thought that acquired hypersensitivity due to repeated doses may have caused an anaphylactic reaction. We also thought there was an acquired hypersensitivity in our patient as there was no history of allergy. However, when we asked insistently, we learned that there was an allergic response to the initial administration of gonadorelin.

GnRH analogues have structural homology. Patients can encounter allergic reactions to more than one GnRH analogue (7). The literature also has a few case reports of anaphylaxis to long-acting GnRH analogues (7, 8). Anaphylaxis usually occurs within 30 min after the exposure. However, approximately half of the patients showed anaphylaxis more than 6 h after the injection of long-acting GnRH analogues (9). Delayed symptoms can be explained by the slow release of the drug. In our patient, anaphylaxis existed immediately upon the

administration of gonadorelin acetate, which is not the depot form. Multiple episodes of anaphylaxis immediately after receiving long-acting GnRH analogues have also been reported (8).

Conclusion

Anaphylaxis due to gonadorelin acetate is a rare but life-threatening side effect. Thus, GnRH analogues must be administered under proper conditions, even if there is no history of systemic hypersensitivity reactions after previous administrations of GnRH analogues.

References

1. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009;123:752–62.
2. Partsch JC, Heger S, Sippel WG. Management and outcome of central precocious puberty. *Clin Endocrinol* 2002;56:129–48.
3. Styne DM, Harris DA, Egli CA, Conte FA, Kaplan SL, et al. Treatment of true precocious puberty with a potent luteinizing hormone-releasing factor agonist: effect on growth, sexual maturation, pelvic sonography, and the hypothalamic-pituitary-gonadal axis. *J Clin Endocrinol Metab* 1985;61:142–151.
4. Potashnik G, Lunenfeld E, Spitz E, Glezerman M. Anaphylactic reaction to gonadotropin-releasing hormone. *N Engl J Med* 1993;328:815.
5. MacLeod TL, Eisen A, Sussman GL. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987;48:500–2.
6. Foster WG, Jarrell JF, Dolovich J, Younglai EV. Immunglobulin-mediated hypersensitivity in response to long term treatment with gonadorelin hydrochloride in a female patient. *Am J Obstet Gynecol* 1989;160:979–83.
7. Ökdemir D, Hatipoğlu N, Akar HH, Gül Ü, Akın L, et al. A patient developing anaphylaxis and sensitivity to two different GnRH analogues and a review of literature. *J Pediatr Endocrinol Metab* 2015;28:923–5.
8. Lam C, Tjon J, Hamilton J, Ahmet AH. Recurrent anaphylaxis associated with gonadotropin-releasing hormone analogs: case report and review of the literature. *Pharmacotherapy* 2006;26:1811–5.
9. Fujisaki A, Kondo Y, Goto K, Morita T. Life-threatening anaphylaxis to leuporelin acetate depot: case report and review of the literature. *Int J Urol* 2012;19:81–4.

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