

Recurrent Anaphylaxis Associated with Gonadotropin-Releasing Hormone Analogs: Case Report and Review of the Literature

Catherine Lam, M.D., James Tjon, Pharm.D., Jill Hamilton, M.D., FRCPC, and Alexandra H. Ahmet, M.D., FRCPC

An 8-year-old girl with idiopathic central precocious puberty experienced multiple episodes of anaphylaxis after receiving a goserelin acetate implant. She was hospitalized and treated with epinephrine, antihistamine, and corticosteroids. The goserelin implant was surgically excised; however, anaphylactic symptoms continued for 4 days after excision. Less severe systemic symptoms recurred 6 weeks after removal; these were possibly due to leakage of the depot drug into subcutaneous tissues. It was noted that 3 years earlier, the patient had developed a similar, milder systemic allergic reaction to leuprolide acetate that required treatment with oral prednisone and antihistamines. Intradermal testing yielded positive results for leuprolide. Gonadotropin-releasing hormone (GnRH) analogs, including leuprolide acetate and goserelin acetate, are commonly prescribed for patients with prostatic carcinoma, endometriosis, and precocious puberty. A literature review identified a single case report of a systemic hypersensitivity reaction involving goserelin acetate and several reports of systemic hypersensitivity reactions associated with leuprolide acetate. We found no reports of systemic reactions to GnRH analogs in pediatric patients. Clinicians should be aware of the potential association of GnRH analogs with systemic reactions. They should also recognize that recurrent anaphylaxis may occur due to the long half-life of these therapeutic agents in tissue.

Key Words: anaphylaxis, hypersensitivity, goserelin, leuprolide, gonadorelin, child, skin tests, precocious puberty.
(*Pharmacotherapy* 2006;26(12):1811–1815)

Gonadotropin-releasing hormone (GnRH) analogs, including leuprolide acetate and goserelin acetate, are commonly prescribed for patients with prostatic carcinoma, endometriosis, and precocious puberty.^{1–5} Sustained levels of GnRH analogs inhibit follicle-stimulating

hormone (FSH) and luteinizing hormone. These agents also exhibit histamine-releasing activity. We found only a few reports in the medical literature that describe systemic hypersensitivity reactions to GnRH analogs, and only one report implicates goserelin acetate in such a reaction.^{6–11} We describe a pediatric patient with a history of systemic allergic reaction to leuprolide, associated with positive intradermal test results, who experienced recurrent anaphylaxis after a course of long-acting goserelin acetate.

Case Report

A 4.5-year-old, previously well girl with no

From the Department of General Paediatrics, University of Toronto, Toronto, Ontario, Canada (Dr. Lam); the Departments of Pharmacy (Dr. Tjon) and Endocrinology (Dr. Hamilton), Hospital for Sick Children, Toronto, Ontario, Canada; and the Department of Endocrinology, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada (Dr. Ahmet).

Address reprint requests to Jill Hamilton, M.D., Department of Endocrinology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

history of allergies was diagnosed with central precocious puberty due to symptoms of breast development, increased growth velocity with advanced bone age, and positive response to a GnRH stimulation test. Magnetic resonance imaging showed normal pituitary anatomy with no evidence of tumor. She was treated with monthly intramuscular injections of leuprolide acetate 7.5 mg. The patient experienced no adverse reactions for the first 6 months of therapy, including no local inflammation at the injection sites. However, 2 weeks after the seventh injection, she developed a suspected allergic reaction with hives, extremity swelling, and polyarthralgia. She responded well to antihistamines and oral prednisone tapered over several weeks. She had no history of exposure to other drugs or identified allergens.

A presumptive diagnosis of leuprolide allergic reaction was made after a positive intradermal test (4–5-mm response) at 1:100 dilution of leuprolide injection without the depot complex, with equivocal response at 1:1000 dilution. A skin-prick test for leuprolide was negative. No available literature provided guidelines for interpreting intradermal or skin-prick testing with leuprolide.

After extensive discussion with the family—focusing on the limited therapeutic options for treatment of central precocious puberty—it was elected to administer a trial dose of goserelin acetate, a different gonadotropin analog. It was not possible to perform skin testing for goserelin acetate as no short-acting preparation of the analog was available in Canada (where the patient lived).

One month later, the patient was administered goserelin acetate depot 3.6 mg/month subcutaneously, with inpatient overnight monitoring for a potential allergic reaction. The family was taught how to use an automatic-injection epinephrine pen at discharge. The patient tolerated the goserelin depot well, with no local or systemic reactions.

Eight months later, she was prescribed the higher dose of subcutaneous goserelin acetate depot—10.8 mg—to be administered every 2 months. The injectable form of this agent is a semisolid cylindrical tube that is placed deep into the abdominal subcutaneous tissue through a large-bore needle. No adverse reactions occurred during the first 35 months of goserelin therapy.

After 3 years of treatment with goserelin, the patient presented to her family physician (5 days after receipt of her most recent goserelin implant)

with hives in a wheal and flare pattern and polyarthralgia, for which she was given a 5-day tapering course of prednisone (which began with approximately 0.4 mg/kg/day). On the last day of the prednisone course, her symptoms flared, and she developed facial swelling and difficulty swallowing. The patient did not have fever, headache, nausea, vomiting, diarrhea, abdominal pain, cough, or visual symptoms.

The patient presented to the emergency department with acute stridor, shortness of breath, and decreased air entry. Her vital signs were stable; she was afebrile and saturating well in room air. Her respiratory symptoms were accompanied by a pruritic blanchable maculopapular rash on her face and extremities, and increasing polyarthralgia and myalgia. Treatment in the emergency department consisted of systemic epinephrine injections administered subcutaneously and intramuscularly, nebulized epinephrine and albuterol, intravenous diphenhydramine, and hydrocortisone. The patient's respiratory symptoms appeared to resolve rapidly with therapy, and she was described as well for approximately 5 hours when similar respiratory symptoms recurred. The goserelin implant was surgically excised in the emergency department less than 3 hours after her first episode of stridor. She was hospitalized for monitoring and investigation.

The patient experienced eight further episodes of recurrent anaphylaxis over the next 4 days, requiring administration of systemic epinephrine, intravenous hydrocortisone, and diphenhydramine every 6 hours. She was monitored in the intensive care unit for 24 hours, where she was given pulse methylprednisolone.

Some of the patient's family contacts had streptococcal throat infections. One week before symptom onset, she had completed a 7-day course of pivampicillin (a penicillin derivative available in Canada), prescribed for suspected bronchitis, which she had previously tolerated. The patient's past medical history was otherwise normal. No developmental concerns were reported. The patient's family history was significant for telangiectasia macularis eruptiva perstans, a form of mastocytosis, in her maternal grandfather and asthma and nut allergy in her mother. No rheumatologic diseases were reported.

Extensive investigations were performed during the patient's hospital admission for rheumatologic, infectious, and inherited immune disorders that might mimic her symptoms of arthralgia, skin rash, and respiratory difficulties. She was negative for antinuclear antibodies and

rheumatoid factor, and her levels of C3, C4, and C1 esterase inhibitors were normal. Her erythrocyte sedimentation rate was 1 mm/hour (normal range 1–10 mm/hr), and C-reactive protein level was 0.2 mg/L (normal range 0–10 mg/L). Her white blood cell count in the emergency department was $17.9 \times 10^3/\text{mm}^3$ (normal range $4\text{--}10 \times 10^3/\text{mm}^3$) with neutrophils $9.12 \times 10^3/\text{mm}^3$ ($0.2\text{--}7.5 \times 10^3/\text{mm}^3$) and bands $0.36 \times 10^3/\text{mm}^3$ ($0/\text{mm}^3$). Throat swabs for *Mycoplasma* and antistreptolysin titers were negative, as were serologies for Epstein-Barr virus, cytomegalovirus, and hepatitis A, B, and C. Luteinizing hormone, FSH, and estradiol levels were suppressed as expected in a patient receiving goserelin. It was not possible to measure serum goserelin levels.

The patient experienced several episodes of sinus tachycardia of unclear etiology during her hospital stay. An echocardiogram revealed a tiny pericardial effusion that resolved on later imaging. The remainder of the cardiac evaluation was negative; the patient had normal 24-hour Holter monitoring, normal blood pressure, normal urine catecholamines, and normal thyroid function tests. Her tachycardia resolved before discharge.

The patient remained on the inpatient ward for 19 days; there were no further episodes of anaphylaxis beyond the first 4 days after goserelin implant removal. A gradual oral prednisone taper was begun in the hospital starting at 30 mg twice/day, with a goal to taper off the corticosteroids over 5 weeks.

One month after discharge, the patient returned to the clinic for follow-up. At that time she was taking prednisone 5 mg/day. She exhibited classic adverse effects from prolonged exposure to corticosteroids, including fatigue, increased appetite, Cushingoid features, striae, and acne. Her mother noted that since the most recent corticosteroid taper, her eyes appeared swollen and a faint pink maculopapular rash emerged over her knees. Her prednisone dosage was then increased to 10 mg/day and thereafter tapered more gradually over 3 months to avoid potential further worsening of her symptoms, with no subsequent recurrence of symptoms.

The patient did not resume therapy to suppress puberty. At a chronologic age of 8.5 years, her breast development was Tanner stage 2 and her pubic hair was Tanner stage 4. (Tanner staging is performed on a scale of 1–5, with 1 indicating no puberty and 5 indicating normal adult female development.) Her height was 143.6 cm and her

bone age was 13 years, giving an estimated final adult height close to the fifth percentile for adult women. There were no further episodes of suspected anaphylaxis over a 1-year follow-up period.

Discussion

This patient's recurrent episodes of cutaneous and respiratory symptoms with response to systemic corticosteroids and antihistamines are most consistent with an immunoglobulin E (IgE)-mediated process. After extensive investigation, recurrent anaphylaxis with urticarial reaction to long-acting goserelin was considered the most likely diagnosis. Idiopathic urticaria, also caused by an IgE-mediated mechanism, is another, although less likely, possibility.

Anaphylaxis and urticarial reactions involve antigen interaction with mast cell and/or basophil-bound IgE antibodies in a process that leads to histamine release, vasodilation, and complement system activation.¹² This cascade of events usually manifests symptoms within 30 minutes of exposure. Symptoms can include feelings of impending doom, difficulty swallowing, dysphagia, chest tightness, stridor, flushing, urticaria, itchy eyes and nose, diarrhea, and hypotension.

Serum sickness was also considered; this is a form of hypersensitivity vasculitis that occurs after administration of foreign antigenic material with formation of antibody-antigen complexes. Symptoms typically occur 7–12 days after antigen exposure, with resolution in 7–10 days. Fever, myalgia, arthralgia, and variable rashes, including urticaria, facial edema, and flushing, are common symptoms. Serum sickness can potentially be IgE mediated, although this is not typical.¹³

We considered two other diagnoses: an allergic reaction to pivampicillin and mastocytosis. An allergic reaction to pivampicillin was deemed unlikely, given the patient's history of having tolerated pivampicillin and other penicillin-related antibiotics, as well as the protracted course and timing of her episodes. Mastocytosis, although unlikely, was considered due to the patient's positive family history. Given her earlier history suggestive of an allergic reaction to leuprolide, the temporal association of her episodes with goserelin administration, and her response to therapy, recurrent anaphylaxis in response to goserelin was considered the most likely diagnosis.

Goserelin acetate has structural homology and cross-reactivity with leuprolide acetate. Both

agents are synthetic analogs of GnRH that inhibit FSH and luteinizing hormone and have histamine-releasing activity. Goserelin is prescribed for precocious puberty, which has an estimated incidence rate ranging from 1:5000–1:10,000.¹⁴ Although GnRH analogs have been used with demonstrated efficacy in central precocious puberty since 1981, the precise number of patients treated with this agent is unknown.

When used for central precocious puberty, goserelin is reported to be effective when given every 9–12 weeks.¹ The half-life of subcutaneous depot preparations of goserelin when administered monthly or every 3 months is reported as 2–4 hours, with no relevant accumulation with repeated depot injections. The depot preparation contains a copolymer matrix impregnated with the drug; this matrix releases the drug at a constant rate for at least 28 days.² However, protracted absorption of depot drugs over longer-than-expected intervals has been described in the literature.⁶ Similarly, leuprolide is available in subcutaneous and intramuscular depot injections to be administered every 1 or 3 months.^{2–5}

Development of an IgE-mediated reaction often requires repeated exposures to an antigen, which may explain why our patient did not react until 3 years into therapy, with continuous antigen exposure during that period.¹⁵ Drug hypersensitivity responses most commonly occur during the first weeks of therapy, but they can emerge at any time.¹⁶ Our patient's symptoms developed 5 days after a depot injection. Although anaphylaxis classically occurs within 30 minutes of exposure, there are exceptions to this rule. In biphasic reactions, an initial reaction may be followed by a second reaction that is more (or less) severe.^{17, 18} Reactions occurring outside the immediate postexposure interval have been described as being accelerated, occurring within hours, or delayed, occurring within days, after exposure.¹⁶

Two possible explanations exist for our patient's delayed presentation of symptoms. First, mild symptoms may have been unrecognized by the family until day 5, when symptoms had progressed to an extent that made them obvious. This scenario is possibly reflective of a second-phase reaction. Alternatively, although the release of depot goserelin acetate is reported to be continuous, exposure to the antigenic protein might not have been significant until day 5 of therapy, when the concentration was sufficient to cause anaphylaxis.

The most perplexing question in this case, as in previous reports, is the protracted course of

the reaction, which necessitated corticosteroid administration long after the depot drug had been removed from the patient. We hypothesize that in addition to delayed absorption and sustained action of the depot preparation, leakage of the depot drug into subcutaneous tissues may allow antigenic material to remain long after the therapeutic effects are complete. Our patient's presentation resembles earlier case reports of anaphylaxis or hypersensitivity to GnRH analogs with respect to onset and duration. These reports support the diagnosis of IgE-mediated anaphylaxis in response to goserelin acetate in our patient.^{6–11}

We know of only one other published case report that describes hypersensitivity to goserelin acetate.⁷ It involved a 36-year-old woman who received monthly subcutaneous injections of goserelin acetate 3.6 mg for treatment of endometriosis. She developed local itching, swelling, and an erythematous skin reaction during her third course of treatment. These symptoms evolved to urticaria, angioedema, tight throat, and shortness of breath with her sixth course of treatment, starting 8 hours after injection. A prednisone taper was given over 12 days. Skin-prick testing was positive for goserelin (1:100,000 dilution) along with latex and allergens, and negative for both the copolymer vehicle and leuprolide. The patient had a history of multiple environmental allergies and asthma. The authors concluded that the reaction was likely IgE mediated, and they questioned whether people with a history of hypersensitivity and atopy with a local reaction at the goserelin implant site should undergo pretesting before starting therapy with goserelin.

Local hypersensitivity to depot leuprolide injection, consisting of erythema and, less commonly, sterile abscess, occurs in up to 5% of children who receive this agent.^{8, 19} However, systemic reactions are extremely rare.^{6, 9} Recurrent anaphylaxis in response to depot leuprolide has been reported in a 27-year-old woman with endometriosis who developed ten episodes of hives and shortness of breath starting 6 hours after receiving depot leuprolide.⁶ These symptoms continued for 2.5 weeks and required treatment with diphenhydramine, epinephrine, and a corticosteroid. The patient had a positive skin test for leuprolide. Six weeks after skin testing, she experienced severe anaphylaxis and recurrent hives, which resolved with a prednisone taper. At the time of anaphylaxis, serum GnRH analog concentrations were undetectable,

and levels of luteinizing hormone, FSH, and estradiol were rising.

Other reports describe anaphylaxis in response to intravenous pulsatile leuprolide therapy. One such report involved a 31-year-old man seen for infertility who developed anaphylaxis after a second intravenous GnRH stimulation test (100 µg), which was performed 10 weeks after his first stimulation test.⁹ This patient had positive results for GnRH on an intradermal skin test.

Finally, two reports describe hypersensitivity to the synthetic GnRH, gonadorelin hydrochloride. The first involves a 28-year-old woman with polycystic ovarian syndrome who experienced anaphylaxis and required intensive care monitoring after her fourth course of treatment (after three uneventful courses).¹⁰ Skin-prick testing was consistent with an IgE-mediated reaction. The second report describes an IgE-mediated urticarial reaction that occurred after 6 months of therapy in a 26-year-old with hypogonadotropic hypogonadism.¹¹

We communicated with the pharmaceutical manufacturer of goserelin acetate, and no further reports of hypersensitivity to the agent were identified (written communication, Medical Information, AstraZeneca Canada, Inc., March 2005).

Conclusion

Systemic hypersensitivity reactions to gonadotropin agonists are a rare but important side effect of therapy. The mechanism of these reactions remains unclear. Of note, in this report and in two previous reports, the reactions were delayed temporally from drug initiation and also from time of last injection. Moreover, the reactions recurred with symptoms, even in the absence of detectable serum drug levels in one patient. The wheal and flare pattern seen in our patient is most consistent with an IgE-mediated reaction. It has been suggested that a small structural variation between natural and synthetic GnRH may lead to an immunogenic response, thus precipitating the reaction.¹⁰

Perhaps the most perplexing aspects of this case and the cases we reviewed are the protracted course of the reaction and the delayed timing of onset. In our patient, the reaction occurred 5 days after her last exposure. A delay of this magnitude is not typical of an IgE-mediated reaction. Goserelin acetate is a depot preparation with delayed absorption and sustained action. Leakage of the depot into subcutaneous tissues may account for both the delayed reaction and

the recurrence of anaphylaxis after surgical excision of the implant. Nevertheless, the mechanism of the protracted course of the reaction remains to be fully elucidated. Until this reaction is fully understood, clinicians should be aware that GnRh analogs can give rise to systemic reactions with the potential for recurrent anaphylaxis over a protracted period of time. In patients with a history of local reaction to GnRH, particularly those with a history of atopy, it may be appropriate to perform skin testing before proceeding with therapy.

References

1. Paterson WF, McNeill E, Reid S, Hollman AS, Donaldson MD. Efficacy of Zoladex® LA (goserelin) in the treatment of girls with central precocious or early puberty. *Arch Dis Child* 1998;79(4):323-7.
2. Repchinsky C. Zoladex® drug monograph. Canadian Pharmacists Association: compendium of pharmaceuticals and specialties. Ottawa, Ontario, Canada: Webcom Ltd, 2005.
3. Repchinsky C. Zoladex® LA drug monograph. Canadian Pharmacists Association: compendium of pharmaceuticals and specialties. Ottawa, Ontario, Canada: Webcom Ltd, 2005.
4. Abbott Laboratories, Ltd. Lupron (leuprolide acetate) product monograph. Montreal, Quebec, Canada; 1999.
5. Abbott Laboratories, Ltd. Lupron Depot (leuprolide acetate depot) product monograph. Montreal, Quebec, Canada; 1999.
6. Lettierie GS, Stevenson D, Shah A. Recurrent anaphylaxis to a depot form of GnRH analogue. *Obstet Gynecol* 1991;78(5 pt 2):943-6.
7. Raj SG, Karadsheh AJ, Guillot RJ, Raj MH, Kumar P. Case report: systemic hypersensitivity reaction to goserelin acetate. *Am J Med Sci* 1996;312(4):187-90.
8. Manasco PK, Pescovitz OH, Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993;123(2):334-5.
9. Potashnik G, Lunenfeld E, Spitz E, Glezerman M. Anaphylactic reaction to gonadotropin-releasing hormone. *N Engl J Med* 1993;328(11):815.
10. MacLeod TL, Eisen A, Sussman GL. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. *Fertil Steril* 1987;48(3):500-2.
11. Foster WG, Jarrell JF, Dolovich J, Young Lai EV. Immunoglobulin-mediated hypersensitivity in response to long-term treatment with gonadorelin hydrochloride (Factrel®) in a female patient. *Am J Obstet Gynecol* 1989;160(4):979-83.
12. Sampson HA, Leung DYM. Anaphylaxis. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson textbook of pediatrics*, 17th ed. Philadelphia: Elsevier Science, 2004:781-2.
13. Sicherer SH, Leung DYM. Serum sickness. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson textbook of pediatrics*, 17th ed. Philadelphia: Elsevier Science, 2004:782-3.
14. Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002;56(2):129-48.
15. O'Dowd LC, Zweiman B. Anaphylaxis in adults. UpToDate. Available from www.uptodate.com. Accessed June 15, 2006.
16. Samel AD. Drug eruptions. UpToDate. Available from www.uptodate.com. Accessed June 15, 2006.
17. Ellis AK, Day JH. Diagnosis and management of anaphylaxis. *Can Med Assoc J* 2003;169(4):307-11.
18. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;95(3):217-26.
19. Neely EK, Hintz RL, Parker B, et al. Two-year results of treatment with depot leuprolide acetate for central precocious puberty. *J Pediatr* 1992;121(4):634-40.