

CASE REPORT

Anaphylactic Reaction to Different Gonadotropin-Releasing Hormone Agonists for the Treatment of Endometriosis: A Case Report

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Abstract: Anaphylactic reactions to gonadotropin-releasing hormone (GnRH) agonists are exceedingly rare, but if they occur, they can be life threatening. This case describes a 33-year-old patient with endometriosis who developed an acute allergic reaction on leuprolide (Lucrin) administration. Although skin tests with the replacement goserelin (Zoladex) were negative, usage of this medication resulted in a similar allergic reaction. This is the first case report that shows that, in case of a proven allergy to one GnRH agonist, a switch to another GnRH agonist should not be made even if allergy tests are negative for this medication.

Key Indexing Terms: Endometriosis; Leuprolide; Goserelin; hypersensitivity; anaphylaxis. [Am J Med Sci 2010;XXX(X):1.]

CASE REPORT

A 33-year-old woman (body mass index, 19.5 kg/m²) visited the Endometriosis Centre of the VU University medical center (Amsterdam, the Netherlands) for a second opinion concerning chronic pelvic pain caused by endometriosis. Her *historia morbi* (Figure 1) started in 2002 with complaints of progressive dysmenorrhea. Consequently, a laparoscopy was performed in 2002 establishing severe endometriosis and an endometriosis cyst in the left ovary. A cystectomy was performed without complications. Postoperatively, medroxyprogesterone (Depo-Provera) intramuscular was advised, which provided excellent pain control. In 2005, hormonal treatment was stopped because of a wish to give birth to a child. Three years later, a spontaneous pregnancy occurred. Four months after childbirth, the menstrual cycle reappeared and was accompanied with progressive dysmenorrhea, dyschezia and chronic pelvic pain. Oral contraceptive use did not improve these complaints. Therefore, she was referred to our centre. After evaluation of her clinical signs and a transvaginal ultrasound showing endometriosis, she was advised to start treatment with a gonadotropin-releasing hormone (GnRH) agonist, leuprolide (Lucrin “PDS Depot,” 3.75 mg) every 28 days, which is the lowest available monthly dosage in the Netherlands.

After the first leuprolide injection, the patient described a “burning, acid feeling” in the abdomen. Two hours after the second leuprolide injection, the patient reported dizziness, confusion with no clear thinking, blurred vision, dysarthria, hyperven-

tilation, shocks all over the body and muscle weakness during a period of 5 hours. In due course, a neurologist in a regional hospital was consulted who related these complaints to a possible adverse effect of the GnRH agonist or alternatively as a vasovagal reaction.

To clarify a possible adverse effect of leuprolide use, we conducted an allergy test to leuprolide and to several other GnRH agonists. The allergy (skin prick) tests in our hospital showed a type 1 allergic reaction to leuprolide with negative reactions to goserelin (Zoladex) or triptorelin (Decapeptyl). The extended European prick test series of volatile allergens and food allergens were also tested but revealed no abnormalities. The skin test reaction to leuprolide is mediated by IgE molecules specific for certain parts of the leuprolide molecule. Interestingly, immediately after the allergy test, the patient developed again dizziness, dysarthria and blurred vision. A consulted neurologist described these complaints as presyncope. Because of these results, leuprolide injections were stopped, and a switch was made to goserelin. After 2 months treatment with goserelin, the endometriosis pain decreased. However, at the third monthly injection of goserelin, a similar systemic allergic reaction occurred as seen before to leuprolide: 5 to 10 minutes after the general practitioner had injected goserelin, the patient became unwell, had a burning feeling in the abdomen, felt weak and hyperventilated and showed a blurred vision and dysarthria. Physical evaluation showed a normal blood pressure of RR 140/85 mm Hg without any signs of a skin rash. After an injection with clemastine (Tavegil), clinical improvement occurred. She was sent home with additional antihistaminic medication if needed. The patient reported that, in both episodes, it was 10 days before she felt normal again: especially her responsiveness was low. The patient described that since the start of leuprolide, she felt extremely tired. Blood tests revealed no abnormalities. Goserelin was stopped and the patient started with oral lynestrenol (Orgametril) 3 tablets of 5 mg/d for 1 month after the last goserelin injection. Up to now, she shows a good therapeutic response to this medication regarding her endometriosis complaints.

DISCUSSION

Recently, a review¹ was published on this topic, which showed a nice overview of 6 cases until 2006. To our knowledge, since 2006 only 1 case report of anaphylaxis to leuprolide was added in 2007.² Our case is the first that shows that, in patients allergic to one GnRH agonist, allergic reactions to other congeners can also occur even with negative skin tests. Hence, switching to another GnRH agonist should be avoided. The adverse drug reaction report form of the Naranjo algorithm shows us that this reaction is a definite adverse drug reaction.³

Earlier in 1987 and 1988, MacLeod et al⁴ and Foster et al,⁵ respectively, described IgE-mediated reactions to lutein-

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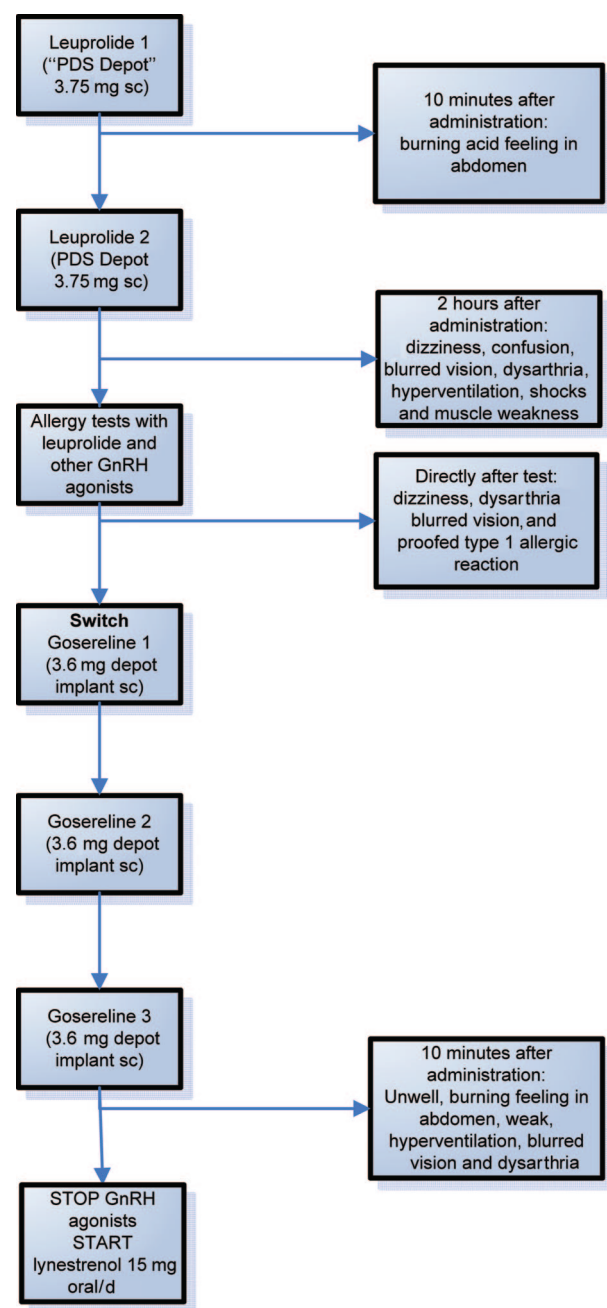


FIGURE 1. Overview of *historia morbi* of this patient starting with the first leuprolide injection.

ing hormone-releasing hormone, when gonadorelin hydrochloride (Factrel) was administered by infusion. These reactions occurred in both cases after 6 months of therapy. Potashnik et al⁶ described a case of a 31-year-old man with severe oligospermia who developed an anaphylaxis after a second intravenous GnRH (Lutrellef) stimulation test. The symptoms of this patient were dizziness, blurred vision and palpitations, followed by hypotension, perspiration and loss of consciousness. Intradermal skin tests with GnRH agonists were positive in the patient. The complaints of this patient are strikingly similar to our patient. These 3 cases show systemic immunological dis-

orders in nondepot GnRH preparations, which means that there is no contribution of particles or anything but likely an allergy to GnRH agonists themselves.

This case is the third allergic reaction against GnRH agonists in a patient with endometriosis. Letterie et al⁷ described a case of a 27-year-old nulliparous woman treated with a 7.5-mg intramuscular depot of leuprolide (Lupron) for her endometriosis. Six hours after injection, generalized hives were developed and, later on, also shortness of breath. Recurrent anaphylaxis occurred and needed immediate and long-term management. Skin tests with leuprolide and gonadorelin hydrochloride produced a positive reaction.

Raj et al⁸ described a case of a 36-year-old woman with endometriosis who developed localized itching, swelling and erythema after the third injection of goserelin. After the sixth dose, a rash developed with the development of swelling in the face, hand and feet and mild dyspnea. After treatment, her symptoms resolved during the following 2 weeks. Skin tests revealed hypersensitivity to goserelin acetate but not to leuprolide. Medication was not switched to leuprolide; hence, it is unknown whether there would have been a reaction in contrast to our case report.

Our report is the second case in literature where a reaction to both leuprolide and goserelin is described. Lam et al¹ described a 4.5-year-old girl with idiopathic central precocious puberty who was treated with leuprolide acetate 7.5 mg intramuscular monthly. Two weeks after the second injection, she developed a suspected allergic reaction with hives, swelling of extremities and polyarthralgia. A skin prick test was negative for leuprolide and not performed for goserelin. Treatment was switched to goserelin acetate 10.8 mg, injected every 2 months. After 3 years, when she was 8 years old, she experienced multiple episodes of anaphylaxis after receiving a goserelin acetate implant.

Case reports on drug-related adverse effects are usually only the tip of the iceberg. How often do these adverse effects really occur? Consulting the Dutch GIP database (an information system of the Health Care Insurance Board, in use since 1988, containing information on expenditure on (extramural) drugs in the Netherlands and the degree to which they are used),⁹ showed us that the most commonly prescribed GnRH agonists in the Netherlands are goserelin (Zoladex), leuprolide (Lucrin) and triptorelin (Decapeptyl) with an increase in the number of prescriptions in the register period 2004 to 2008 (Table 1).

Treatment of endometriosis in our clinic is primarily done with leuprolide and in some cases goserelin. Table 1 shows the share in the market of different GnRH agonists in the Netherlands not specified for endometriosis (main indication is prostate cancer).

To investigate how often adverse immunological reactions are present in combination with GnRH agonist use in the Netherlands, we contacted Lareb (Nederlands Bijwerkingen Centrum Lareb),¹⁰ the Dutch Pharmacovigilance Centre that registers data on adverse drug reactions. These data are collected from medical doctors, patients and pharmaceutical com-

TABLE 1. Numbers of patients using GnRH analogs 2004–2008 in the Netherlands in general⁹

	2004	2005	2006	2007	2008
Leuprolide (Lucrin)	7,864	8,088	8,495	8,904	11,205
Goserelin (Zoladex)	13,128	13,232	14,962	14,899	15,638
Triptorelin (Decapeptyl)	6,193	6,213	5,926	8,983	9,824

TABLE 2. Reports of LHRH (luteinizing hormone releasing hormone) analogs and "immune systems disorders" 1988–2010 of WHO (97 countries)¹¹

Drug	Reaction	No. reports	
Buserelin	Anaphylactic shock ^a	3	3
	Serum sickness ^b	1	
	Hypersensitivity ^c	7	
Goserelin	Anaphylactic shock ^a	5	8
	Anaphylactic reaction ^b	3	
	Type IV hypersensitivity reaction ^c	1	
	Hypersensitivity ^c	21	
Leuprolide	Anaphylactic shock ^a	7	34
	Anaphylactic reaction ^d	4	
	Anaphylactoid reaction ^e	23	
	Serum sickness ^b	6	
	Multiple allergies	1	
	Hypersensitivity ^c	66	
Triptorelin	Allergy to metals	1	6
	Anaphylactic shock ^a	3	
	Anaphylactic reaction ^d	2	
	Anaphylactoid reaction ^e	1	
Total	Hypersensitivity ^c	5	51
		160	

Definitions conform Lareb.

^a Anaphylactic shock: hypersensitivity reaction with clinical signs in 2 or more organ systems with low blood pressure.

^b Serum sickness: serum sickness is a reaction similar to an allergy. Specifically, it is an immune system reaction to certain medications, injected proteins or antiserum.

^c Hypersensitivity: symptoms being an expression of hypersensitivity.

^d Anaphylactic reaction: hypersensitivity reaction with clinical signs in 2 or more organ system without low blood pressure.

^e Anaphylactoid reaction: nonallergic anaphylactic shock or reaction.

panies. Information of Lareb is also only the tip of the iceberg, but it provides an impression on how often (severe) adverse effects occur.

From 2001 until February 2010, there are 6 cases of "immune system disorders" reported by Lareb in the Netherlands. Four cases are caused by triptorelin, 1 for goserelin and 1 for leuprolide. Our patient is the reported case of leuprolide.

This information indicates that immune system disorders according to GnRH agonists use are extremely rare in the Netherlands. This made us look into the World Health Organization data on worldwide use of GnRH agonists.

Table 2 shows World Health Organization data¹¹ on luteinizing hormone-releasing hormone analogs of 97 countries of adverse effects on the immune system worldwide from 1988 till March 2010. It is interesting to compare these different GnRH agonists' data with each other although it is unknown what market share these products have worldwide. Table 2 shows that leuprolide has more than two thirds of all immune systems disorders compared with buserelin, goserelin and triptorelin, even if only looking at anaphylactic shock reaction and anaphylactoid reaction. It should be noted that causality is not always clear in these cases, because these data can be reported not only from trials but also by the patients themselves. These data definitely show that there are more immune system disorders than can be found in the literature.

What can be Learned from All This?

As Raj et al⁸ have already questioned, in case of a proven GnRH agonist allergy, whether a switch to another GnRH agonist should be made when the results of the skin tests are negative. Our case gives an answer to this question.

The molecular structure of leuprolide and goserelin are similar. This can lead to cross reactivity of IgE antibodies, but it is unknown to which extent. Therefore, we advise not to switch to another agonist in case of a proven allergy to a GnRH agonist.

Anaphylaxis is an incidental side effect of GnRH agonists, which can be life threatening. Because the reaction is Ig E mediated, there has to be a sensitization time and exposure to the medicine. The case report of Lam et al¹ shows this sensitization time very clearly.

A negative test result cannot predict future development of allergic reactions. Hence usage of structurally related congeners can easily result in similar adverse reactions and therefore not to be done.

CONCLUSION

Anaphylactic reactions to GnRH agonists are exceedingly rare but can be life threatening. This case describes a 33-year-old woman who developed a type I-mediated reaction to leuprolide. Although skin tests with goserelin revealed no abnormalities, a similar reaction was developed to this medication in the same patient. This is the first case report that shows that, in case of a proven allergy to GnRH agonists, a switch to another GnRH agonist should not be made even if an allergy test is negative to the alternate GnRH agonist.

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