Original Article

Evaluation of Hypersensitivity Reactions with Leuprolide Acetate and Triptorelin Acetate in Children

Azize Pınar Metbulut, Keziban Toksoy Adıgüzel[1], Candan İslamoğlu, Mehmet Boyraz[1,2], Emine Dibek Mısırlıoğlu

Division of Pediatric Allergy and Immnunology, [1]Division of Pediatric Endocrinology, University Health of Science, Ankara City Hospital, [2]Department of Pediatric Endocrinology, Ankara Yıldırım Beyazıt University, Ankara, Turkey

Abstract

Introduction: Gonadotropin releasing hormone analogues (GnRHa) are commonly used to treat central precocious puberty (CPP). Generally, they are well-tolerated; however adverse reactions have been reported. Local adverse events occur in 10-15% of the patients who were treated with GnRHa. Anaphylactoid reactions with GnRHa are very rarely seen. The aim of this study is to report our clinical experience with hypersensitivity reactions seen in pediatric patients receiving leuprolide acetate (LA) and triptorelin acetate (TA) in CPP at the single pediatric tertiary medical center and to evaluate the incidence rate of hypersensitivity reactions. **Methods:** This retrospective study included children with CPP who were treated with GnRHa (LA and TA) at our hospital between January 2013 and December 2020. We analyzed clinical characteristics of patients who experienced adverse reactions and analyzed the incidence rate. **Results:** Seven side effects (adverse reactions) (0.69%) were observed among total of 1010 CPP patients who were treated with TA and LA. Sterile abscesses were observed in 3 patients (0.29%). None of the patients had an anaphylaxis. Tremors of both hands, a vomiting episode, an urticarial rash, and musculoskeletal stiffness were observed in one patient each. **Conclusion:** In our study, mild reactions were seen in 7 patients. GnRHa can be safely used and well-tolerated medications; but exceedingly rare, severe reactions can be developed.

Keywords: Adverse reactions, central precocious puberty, drug hypersensitivity reaction, gonadotropin-releasing hormone analogues

Introduction

Leuprolide acetate (LA) and Triptorelin acetate (TA) are synthetic nonapeptides that are potent gonadotropin-releasing hormone receptor (GnRH) agonists that acts via downregulation of GnRH receptors on pituitary. They are used in the management of a variety of diseases including central precocious puberty (CPP) in childhood and prostate cancer, breast cancer, endometriosis, uterine fibroids, and in-vitro fertilization techniques in adults.[1-3]

CPP is a rare disease (1:5000 to 1:10.000) and is characterized by the onset of secondary sexual characteristics in females who are younger than 8 years age and in males younger than 9 years age, as a result of early maturation of the hypothalamic-pituitary-gonadal axis.[1,4] The aims of the treatment are as follows: preventing early menarche, maintenance of normal body proportions and height growth, physical and psychological levels including ensuring social/mental well-being.[1]

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Adverse drug reaction (ADR) is a harmful, unintentional, and undesired response to a drug that occurs while using in humans for diagnosis, prophylaxis, and treatment.[5] Adverse drug reaction is classified into two types: A-type (predictable) and B-type (unpredictable) reactions. Type A reactions are the result of the pharmacological action of the drug and therefore they are dose-dependent and predictable. Type B reactions are unpredictable, usually, non-dose-dependent, seen in sensitive patients, often are severe, and carry a risk for mortality and morbidity.[6] Drug hypersensitivity reactions (DHRs) are Type B reactions. DHR can be allergic or non-allergic.

Address for correspondence: Prof. Emine Dibek Mısırlıoğlu, Ankara City Hospital Department of Pediatrics Division of Pediatric Allergy and Immunology, Ankara, Turkey.
E-mail: edibekm@yahoo.com

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Allergic reactions are commonly IgE-mediated (type I) and T-cell mediated (type IV). Rarely, they are mediated by cytotoxic (type II) and immune complex reactions (type III).[7]

Despite being well-tolerated by most of the patients, hypersensitivity reactions in a small proportion of cases receiving LA and TA have been reported in the literature.[4,8] Local reactions with induration and aseptic abscess at the injection site are well known.[9] In addition to local reactions, cases of anaphylaxis have been reported in a small number of patients.[2,4,9-13]

There are limited studies in the literature about hypersensitivity reactions associated with GnRHa in children. The aim of this study is to report our clinical experience with hypersensitivity reactions seen in pediatric CPP patients receiving LA and TA at a single pediatric tertiary medical center and to evaluate the prevalence rate of adverse reactions.

Methods

This is a retrospective review of children who were diagnosed with CPP and treated with LA (Lucrın Depot-Ped® 3,75–7,5 mg/monthly or 11.25–30 mg/3 monthly intramuscular [IM]) and TA (Decapeptyl® 3,75–7,5 mg/monthly IM) in the Pediatric Endocrinology between January 2013 and December 2020. The study protocol was approved by the Institutional Ethics Committee of Ankara City Hospital (E2-21-98).

Medical records were reviewed retrospectively. Medical history and demographic information regarding age, gender, patient history, the medication type of GnRHa used for CPP, age at initiation of treatment, injection dose, and interval, the duration of treatment and if patients had a hypersensitivity reaction to treatment, information about hypersensitivity reactions such as the onset of occurrence of ADR, the clinical course of ADR and treatments that were given for allergic reactions, and whether having a chronic disease were noted.

Definition of central precocious puberty

The criteria for the diagnosis of CPP and initiation of GnRH analog treatment were as follows: breast development > Tanner stage II starting before 8 years of age, menarche before 9.5 years age, basal LH >0.2 U/L or stimulated LH level above 5.0 IU/L, long diameter of the uterus >30 mm, advanced bone age and rapidly progressing puberty with the decline in predicted adult height. GnRH analog treatment was considered in patients with rapid progression of puberty.[8]

In our country, LA and TA are available; however, there have been periods of interruptions in TA or LA supply over the study period, causing switching to the available one.

Evaluation of the drug hypersensitivity reactions

The drug allergy work-up started with the standardized European Network for Drug Allergy (ENDA) questionnaire on drug allergy. Reactions that occurred within the first and 6 hours were labeled as 'immediate reactions', commonly manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis. 'Non-immediate reations' occured any time from 6 hour, commonly after many days of treatment. Non-immediate reactions usually manifested with exanthemas and delayed urticaria. In non-immediate reactions, internal organs can also be affected. Diagnosis of DHRs is primarily based on a detailed clinical history and *in vivo* procedures, such as skin testing (ST) and drug provocation tests (DPT).[14] If the history of the reaction is compatible with drug hypersensitivity, then skin tests and DPTs with the suspected drug can be performed. When skin tests are negative and there is no contraindication, provocation with the suspected drug can be performed according to ENDA guidelines.[15-17] However, skin tests and provocation tests were not performed in our patients with DHRs due to discontinuion of their GnRHa treatment and refusal by the patients' parents/guardians to perform the diagnostic tests.

Sterile abscess was defined as a condition in which infectious etiology cannot be shown.[18]

Statistical analysis

Results were expressed as a percentile (absolute numbers), as mean and standard deviation, or as median and interquartile range (IQR) as required. SPSS 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

A total of 1010 GnRHa-treated CPP patients, including 93.9% (n: 948) girls, were evaluated. The median age of the children at the beginning of the treatment was 8 years (IQR 98-113). 11.4% (n: 115) of the patients had additional chronic disease and the commonest chronic disease was hypothyroidism with a rate of 2.5% (n: 25)

Patients who were treated with only TA and only LA were 61.2% (n: 618) and 36% (n: 364) of the patients respectively. 2.8% (n: 28) of the patients switched treatment to TA or LA because of interruptions in TA or LA supply.

Patients treated with GnRHa monthly and per 3 months were 91.1% (n: 920) and 8.9% (n: 90) respectively. The mean age of the treatment onset was 105.5 months. 87.3% (n: 882) of the patients were given treatment at 3.75 mg/month, 3.8% (n: 38) of the patients were given treatment at 7.5 mg/month and 8.9% (n: 90) of the patients given at 11.25 mg/3 monthly [Table 1].

There was 5 (0.49%) hypersensitivity reaction and 2 (0.19%) adverse reactions among 1010 patients [Table 1]. The prevalence of adverse reactions calculated by using the respective number of patients using TA or LA as denominator, was 0.006% with TA and 0.007% with LA.

The median age of the patients who had adverse reactions was 8 years and 6 months (IQR 95.7-108). The observed adverse reactions and hypersensitivity reactions were urticarial rash, vomiting, tremor of both hands, sterile abscesses, and musculoskeletal stiffness.

Table 1: Characteristics of the patients with precocious puberty developing adverse reaction

Patient number	Age at the beginning of the treatment (years)	Gender	Additional Chronic Disease	GnRHa depot	Dose of GnRHa	Number of the injection at the time of reaction and interval between the reaction	Symptoms	Continuation of the treatment	Reaction type	Who causality assesment scale
1	8.5	F	-	TA	3.75 mg/month	20th and 21st Immediately after	Tremor at both hands	Discontinued	Adverse reaction	Probable/likely
2	9	F	-	TA	3.75 mg/month	11th Immediately after	Vomiting	Discontinued	Hypersensitivity reaction	Possible
3	7.5	F	-	TA	3.75 mg/month	1st 72 hour after	Urticarial rash	Discontinued	Hypersensitivity reaction	Probable/likely
4	8	M	Bipolar disease, Autism spectrum disorder, hypothyroidism	LA	3.75 mg/month	9th 1 week later	Sterile abscess	Switched to TA treatment	Hypersensitivity reaction	Probable/likely
5	8 years 9 month	F	-	LA	3.75 mg/month	4th 10 days later	Sterile abscess	Switched to TA treatment	Hypersensitivity reaction	Probable/likely
6	7 years 11 month	F	-	LA	3.75 mg/month	3rd 1 week later	Sterile abscess	Switched to 11.25 mg per 3 month	Hypersensitivity reaction	Probable/likely
7	10 years 1 month	M	-	TA	3.75 mg/month	5th Immediately after	Musculoskeletal stiffness	Discontinued	Adverse reaction	Probable/likely

None of the patients had a history of allergic drug reactions before. Only 1 patient had an additional chronic disease (Bipolar disorder, autism spectrum disorder, and hypothyroidism).

Four of the patients' treatments were discontinued due to reaction. In 3 of them, treatment can be continued via switching to another GnRHa or regulating dosage with the same drug [Table 1].

Case summaries

Case 1

An 8.5-year old girl without having any chronic disease, presented with rapidly progressive CPP. Triptorelin acetate depot was initiated at a dose of 3.75 mg monthly. Following the 20th and 21st dose of treatment, she developed tremors in both hands immediately after administration of TA. Before the 20th dosage, no symptom had been seen after administration of treatment. GnRHa was discontinued. She was evaluated by the neurology department. Her laboratory tests for thyroid disease, Wilson disease, and cranial magnetic resonance imaging (MRI) were evaluated and reported to be normal. After termination of TA treatment, her symptom was improved spontaneously.

Case 2

A 9-year old girl without having any chronic disease, presented with rapidly progressive CPP. She was initiated on TA treatment at a dose of 3.75 mg monthly. Following the 11th dose of TA, she had vomiting immediately after the injection. She did not have any other system symptoms. Her physical examination and blood pressure were normal. Vomiting symptom was improved spontaneously. During the first 10 TA injections, there were no symptoms. Treatment was discontinued after this reaction.

Case 3

A 7.5-year old girl without having any chronic disease, presented with CPP and was initiated TA treatment at 3.75 mg per month. She developed disseminated urticarial rashes 72 hours after the first injection of triptorelin acetate treatment. Except for urticaria, her physical examination was normal. Rashes regressed in 10 days by using the antihistaminic treatment. TA treatment was discontinued. The tests for diagnosis of hypersensitivity to GnRH could not be performed cause of termination of the drug by an endocrinologist and the patient's parents not giving the permission.

Case 4-5-6

There cases initiated LA treatment at 3.75 mg per month with a diagnosis of CPP and developed sterile abscesses at 9th, 4th and 3rd dose of LA treatment respectively. In two of the patients, LA treatment was switched to TA treatment and no further symptom were observed. In one of the patients, LA treatment switched to LA treatment at 11.25 mg per month and no further symptom was observed. All of them are still being treated with GnRHa treatment [Table 1].

Case 7

A 10-year and 1 month old male patient without having any chronic disease, presented with rapidly progressive puberty and

initiated TA treatment. Following the 5th dose of TA treatment, he had developed difficulty in walking due to stiffness in the leg immediately after injection. The spasm lasted all day at the injection day. The treatment was discontinued.

Discussion

Of the 1010 patients, only 7 patients had adverse reactions and hypersensitivity reactions with TA and LA. The observed adverse reactions and hypersensitivity reactions were an urticarial rash, vomiting, tremor at both hands, sterile abscesses formation, and musculoskeletal stiffness.

GnRHa is generally well-tolerated; however adverse reactions have been reported in association with GnRHa from local skin irritation to severe anaphylactoid reactions. Local adverse events occur in 10-15% of the patients who were treated with GnRHa. Anaphylactoid reactions with GnRHa are very rarely seen; but if they occur, they can be life-threatening.[19]

According to Cheung and *et al*.,[20] there was no difference between triptorelin acetate and leuprolide acetate in terms of their side effects. The prevalence of adverse reactions calculated by using the respective number of patients using TA or LA as denominator, was 0.6% with TA and 0.7% with LA.

Adverse reactions reported to be associated with LA are as follows: hot flashes and diaphoresis, testicular atrophy, gynecomastia, erectile dysfunction, pituitary apoplexy, osteoporosis. Adverse events reported in post-marketing surveillance are as follows: Anaphylactoid reactions or asthmatic process (incidence rate of about 0.002%), fibromyalgia, photosensitivity reactions, rash (unspecified), respiratory disorders, seizures, urticaria, and weight gain.[3]

According to Lee and *et al*.,[4] among the total of 621 CPP and early onset puberty children with long-acting gonadotropin-releasing hormone agonists therapy, side effects were observed in 6 (0.9%) of the patients. In 3 of these patients, sterile abcess formations were observed with LA and after the reaction, treatment switched to the TA. In our study, also 3 of the patients developed sterile abscess with LA and treatment can be continued via switching to the TA in 2 patients and changing the dose of LA to 11.25 mg per 3 months in 1 patient. These patients can be continued their treatment without any symptom. These sterile abscess formations were observed only with patients who were treating with LA. This finding may show a higher possibility of sterile abscess formation with LA therapy than TA therapy. In a study, it was reported that sterile abscess formation was associated with polymer in depot leuprolide acetate.[21]

According to Yasukawa and *et al*.,[22] after LA injection, subcutaneous nodules at injection sites which skin biopsy showed a granulomatous reaction, were reported. None of our patients had subcutaneous nodules at injection sites.

In the literature, severe immediate hypersensitivity reactions are reported in children.[9,13] There are also adult case reports with ADR with GnRHa.[23] In half of the patients who were reported to have anaphylaxis, it was found that anaphylaxis was seen 6 hours after the injection. This can be explained by the slow and sustained release of the drug with GnRHa.[2,4,9-13] In our study, none of the patients had anaphylaxis with GnRHa.

In the literature, there are also rare cases with LA adverse drug effect. A case of fixed drug eruption, leukocytoclastic vasculitis, serum sickness, generalized papular erythroderma, and unilateral slipped femoral epiphysis have also been reported in adult patients with LA.[3,22,24-26] None of our patients had these findings.

In the literature, there are limited reports about adverse drug effects of TA. According to Carel and *et al*.,[27] in 64 patients triptorelin at a high dose of 11.25 mg/month was well-tolerated. Headache was observed as the most frequent adverse event in 17% of the girls and 40% of the boys. Mild to moderate rhinitis, abdominal pain, gastroenteritis, and rash were also reported in 13%, 9%, 5%, and 5% of the patients respectively. According to Lee and *et al*.,[4] in 1 patient, anaphylaxis was developed with TA. In Decapeptyl prescription, tremor and musculoskeletal stiffness were also reported as ADR.[28] In our study, 4 patients had reactions with TA as follows: tremor, vomiting, urticarial rashes, and musculoskeletal stiffness. In our study, the theraphy was discontinued in patients having vomiting and musculoskeletal stiffness however in these situations, the option of considering continuation of therapy can be conceivable.

In a study from Turkey, between 2015 and 2019, in 232 patients with precocious puberty receiving GnRHa treatment, 9 (3.8%) of the patients developed systemic hypersensitivity reactions. 6 of these reactions developed on TA, 3 of them developed on LA treatment and 1 of them developed with both medications who developed an urticarial rash with TA and also developed anaphylaxis with LA during the intradermal test. Patients developed urticarial, pruritus, angioedema, and skin lesions suggestive of HSP.[8]

There are differences in additives or stabilizing agents in GnRHa that may be causing hypersensitivity reactions.[8] In the patient who had reactions to both GnRHa, reactions to additives should be investigated.

Due to cases that were shown cross-reactivity between two different GnRHa, before switching the medication to the other analogs, skin tests with alternative medications should be done.[8,9] Since depot forms of GnRH analogs contain more content than the active drug, it should be kept in mind that such commercial preparations may be exceeding the concentration of irritants on the skin for IDT and SPT. This problem causes difficulty in evaluating tests and a lack of data in the literature. Hence, there are only a few reports of skin test results with GnRH analogs.[8]

If it is essential to use the GnRH that caused hypersensitivity reaction and alternative therapeutic options are not available, desensitization protocols can be used.[29]

The limitation of our study is that this study was retrospective and allergy diagnostic tests were not performed to confirm the hypersensitivity reaction in patients.

Conclusion

In our study, mild reactions were seen in 7 patients. None of the patients had an anaphylactic reaction. GnRHa can be safely used and well-tolerated medications; but exceedingly rare, severe reactions can be developed. All patients receiving GnRHa treatment should be carefully monitored for hypersensitivity reactions.

Statement of ethics

The study protocol was approved by the Institutional Ethics Committee of City Hospital (E2-21-98). Written informed consent was obtained from the patient's parents for publication of the details of their medical case.

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Conflicts of interest

There are no conflicts of interest.

References

1. Wilson AC, Meethal SV, Bowen RL, Atwood CS. Leuprolide acetate: A drug of diverse clinical applications. Expert Opin Investig Drugs 2007;16:1851-63.
2. Fujisaki A, Kondo Y, Goto K, Morita T. Life-threatening anaphylaxis to leuprorelin acetate depot: Case report and review of the literature. Int J Urol 2012;19:81-4.
3. Gnanaraj J, Saif MW. Hypersensitivity vasculitis associated with leuprolide (Lupron). Cutan Ocul Toxicol 2010;29:224–7.
4. Lee JW, Kim HJ, Choe YM, Kang HS, Kim SK, Jun YH, *et al*. Significant adverse reactions to long-acting gonadotropin-releasing hormone agonists for the treatment of central precocious puberty and early onset puberty. Ann Pediatr Endocrinol Metab 2014;19:135-40.
5. Dona I, Salas M, Perez-Sanchez NI, Aguilar C, Torres MJ. Phenotypes and natural evolution of drug hypersensitivity. Curr Treat Options Allergy 2019;6:27-41.
6. Kendirci HN, Ağladıoğlu SY, Baş VN, Önder A, Çetinkaya S, Aycan Z. Evaluating the efficacy of treatment with a GnRH analogue in patients with central precocious puberty. Int J Endocrinol 2015;2015:247386.
7. Fernandez J, Dona I. Diagnosing and managing patients with drug hypersensitivity. Expert Rev Clin Immunol 2018:14:29-41.
8. Kirkgoz T, Karakoc-Aydiner E, Bugrul F, Yavas Abali Z, Helvacıoğlu D, Kiykim A, *et al*. Management of systemic hypersensitivity reactions to gonadotropin-releasing hormone analogues during treatment of central precocious puberty. Horm Res Paediatr 2020;93:66-72.
9. Ökdemir D, Hatipoğlu N, Akar HH, Gül Ü, Akın L, Tahan F, *et al*. A patient developing anaphylaxis and sensitivity to two different GnRH analogues and a review of literature. J Pediatr Endocr Met 2015;28:923-5.
10. Letterie GS, Stevenson D, Shah A. Recurrent anaphylaxis to a depot form of GnRH analogue. Obstet Gynecol 1991;78:943-6.
11. Taylor JD. Anaphylactic reaction to LHRH analogue, leuprorelin. Med J Aust 1994;161:455.
12. Grant JP Jr, Levinson AW. Anaphylaxis to leuprolide acetate depot injection during treatment for prostate cancer. Clin Genitourin Cancer 2007;5:284-6.
13. 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.
14. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, *et al*. *In vitro* tests for drug hypersensitivity reactions: An ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2016;71:1103-34.
15. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002;57:45-51.
16. Brockow K, Garvey LH, Aberer W, Atanoskovic-Markovic M, Barbaud A, Bilo MB, *et al*. Skin test concentrations for systemically administered drugs—An ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013;68:702-12.
17. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, *et al*. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. Allergy 2003;58:854-63.
18. Kaya A, Yıldız Kaya S. A case of recurrent sterile abcesses following tetanus-diphteria vaccination treated with corticosteroids. BMC Infect Dis 2021;21:53.
19. Carel JC, Blumberg J, Seymour J, Adamsbaum C, Lahlou N, Triptorelin 3-month CPP study group. Three-month sustained-release triptorelin (11.25mg) in the treatment of central precocious puberty. Eur J Endocrinol 2006;154:119-24.
20. Cheung TH, Lo KW, Lam CW, Lau W, Lam PK. A crossover study of triptorelin and leuprolin acetate. Fertil Steril 2000;74:299-305.
21. Johnson SR, Nolan RC, Grant MT, Price GJ, Siafarikas A, Bint L, *et al*. Sterile abscess formation associated with depot leuprolide acetate theraphy for central precocious puberty. J Paediatr Child Health 2012;48:E136-9.
22. Yasukawa K, Sawamura D, Sugawara Kato N. Leuprorelin acetate granulomas: Case reports and review of the literature. Br J Dermatol 2005;152:1045-7.
23. Lüchinger AB, Mijatovic V, Rustemeyer T, Hompes PG. Anaphylactic reaction to different gonadotropin-releasing hormone agonists for the treatment of endometriosis. Am J Med Sci 2011;341:240-2.
24. Salins CA, Kupfer-Bessaguet I, Fleuret C, Staroz F, Plantin P. Fixed drug eruption induced by leuprorelin. Ann Dermatol Venereol 2015;142:780-1.
25. Turk BG, Dereli T, Dereli D, Akalın T. Leuprolide acetate-induced leukocytoclastic vasculitis. Acta Obstet Gynecol Scand 2007;86:892-6.
26. Burris K, Ding CY, Lim GF. Leuprolide acetate-induced generalized papular eruption. J Drugs Dermatol 2014;13:755-7.
27. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH analogs consensus conference group, *et al*. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.
28. Available from: https://www.medicines.org.uk/emc/product/2229/smpc#gref.
29. Chan Ng P, Huang CH, Rajakulendran M, Tan MM, Wang PP, Tay LQ, *et al*. Successful desensitization to gonadotropin-releasing hormone analogue triptorelin acetate using a sustained-release depot preparation. Pediatr Allergy Immunol 2018;29:660-3.