Journal of Population Therapeutics & Clinical Pharmacology

Safety of GnRH Agonist in Female Children and Adolescents with Central Precocious Puberty

Hussain T. Bakhsh[1], Reem M. Diri[1], Daniah E. AlMohammady[2], Lujain S. Alklaikh[2], Shoug S. Alnefaie[2], Hadeel M. Banasser[3], Asma A. Alqasimi[3], Asmaa J. Akbar[3], Abdulrahamn S. Aljuaid[3], Mohammed A. Alamri[3]

[1] Associate Professor, Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

[2] Pharm.D. Candidate, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

[3] Registered Pharmacist, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Corresponding Author:

Hussain T. Bakhsh, Associate Professor, Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

Email: htbakhsh@kau.edu.sa

ORCID: 0000-0001-5374-3017

ABSTRACT

Background: Central Precocious Puberty (CPP) is characterized by the premature activation of the hypothalamic-pituitary-gonadal axis, causing early puberty in children. Gonadotropin-releasing hormone analog (GnRH-a) has been approved for treating CPP. However, limited studies have evaluated its safety among Saudi residents. Thus, our goal is to assess the safety of this treatment for Saudi female children and adolescents aged 6 to 14 years.

Methods: From September 2022 to March 2023, a cross-sectional study was carried out at the Pediatric Endocrine Clinic at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The study involved 148 female participants, aged 6-14, who were administered GnRH-a. The main objective was to assess the most prevalent adverse drug reaction (ADR) in children dealing with CPP.

Results: Out of 148 patients, 18.9% reported no ADRs from GnRH-a treatment. The most common ADRs were injection site pain (50.7%) and mood swings (45.3%), followed by weight gain (35.8%), increased appetite (29.7%), and abdominal pain (18.2%). Bone pain affected 14.9% of the patients. Allergic reactions, vaginal bleeding, and bruising were less commonly reported, affecting 9.5%, 2.0%, and 2.7% of patients, respectively.

Conclusion: While GnRH-a has several ADRs, none of the patients perceive these effects as determining their treatment course. However, factors like the high cost and limited availability of the medication prevented some from completing the therapy.

Keywords: Early puberty, gonadotropin-releasing hormone agonists, Saudi Arabia

INTRODUCTION

Central precocious puberty (CPP) is a condition characterized by the premature activation of the hypothalamic-pituitary-gonadal axis (HPGA). This leads to an increased production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are crucial for female sexual development and functioning. They regulate the menstrual cycle and stimulate egg formation in the ovaries [1,2]. This process, consequently, increases estrogen production, which is converted into estradiol. Therefore, this triggers the early development of pubertal features, such as breast enlargement and the growth of pubic and underarm hair [1]. Although the cause of CPP is predominantly idiopathic, accounting for 90% of cases in females, it is important to note that girls are ten times more likely to be affected than boys [1,3].

Precocious puberty typically affects girls prior to reaching 8 years old, though it generally occurs between 8 and 14 years old. A common indicator of a child's development is their height. Many factors, including puberty, can influence a girl's height throughout adolescence and childhood [4].

Puberty is a physiological process in human development that takes place during adolescence. It triggers cognitive and physical growth, fast-tracking growth and bone maturation. This leads to the fusion of the epiphysis and the attainment of final height [5].

The second characteristic is the onset of menstruation, or menarche, which occurs 1 to 6 years after puberty begins. Early menarche can lead to delayed development and heights below the typical adult height, resulting in the girl growing up shorter in stature [4].

Menarche is significantly influenced by various factors such as genetics (including maternal age at menarche), metabolism, body mass index (BMI), nutrition, environmental factors [6], and hormone-mimicking substances (xenoestrogens). These can either increase endogenous estrogen secretion or exhibit estrogenic effects [6,7].

A previous study in South Korea revealed that between 2008 and 2014, 1,220 boys and 37,890 girls were newly diagnosed with CPP. During the study period, per 100,000 individuals, there were 262.8 cases in girls and 7.0 cases in boys. The overall prevalence of CPP was 193.2 per 100,000 people (410.6 for girls and 10.9 for boys). Both the frequency and incidence of CPP have significantly increased in boys and girls over the study period [8].

A long-acting gonadotropin-releasing hormone agonist (GnRH-a) is the foundation of CPP treatment. It inhibits the HPGA by reducing the sensitivity of pituitary gonadotrophs. Its effects consist of managing pubertal symptoms and extending the developmental stage. This is achieved by reducing growth to prepubertal hormonal levels and delaying the advancement of bone age [1,9].

Of the 621 patients studied, 469 girls (average age: 8.78 ± 0.45 years) were administered monthly depot leuprolide acetate, while 152 girls (average age: 8.35 ± 0.47 years) received monthly depot triptorelin acetate. Significant medication side effects occurred in six cases, affecting five female patients (0.9% of the total group). Four patients (0.6%) developed a sterile abscess due to the GnRH-a injection. In a separate case, one patient experienced anaphylaxis, and another had unilateral slipped capital femoral epiphysis [10].

In addition, a clinical trial involving 307 CPP patients found that most of them responded well to GnRH-a treatment, and the incidence of adverse drug reactions (ADRs) was low (>2%), with the most common ones being injection site induration (4.6%) and vaginal bleeding (2.3%) [11].

Studies evaluating the safety of GnRH-a in Saudi Arabia are presently scarce. To our understanding, this will be the first one. Consequently, this study aims to explore the safety of GnRH-a treatment in Saudi female children and adolescents aged 6 to 14.

METHODS

Study design

From September 2022 to March 2023, a cross-sectional study was conducted at the Pediatric Endocrine Clinic of the outpatient department at KAUH in Jeddah, Saudi Arabia. This study included 148 female patients, ages 6 to 14 years, who were administered GnRH-a.

Study participants

During the study period, we assessed 156 female patients for eligibility. We included female children and adolescents aged 6-14 years undergoing puberty progression who had received GnRH-a (Triptorelin injection) treatment for at least 6 months; these accounted for 148 of our study participants. We excluded eight participants for the following reasons: treatment duration of less than 6 months, male gender, or diagnosis of pathological CPP.

Ethical approval

The study was authorized by the Biomedical Ethics Committee of KAUH on February 20, 2023 (Ref.# HA-02-J-008). We secured written and verbal consent from each participant or their caregiver. We conducted all methods according to applicable guidelines and regulations.

Outcome

The primary objective of this study is to evaluate the safety of GnRH-a by analyzing the most common ADRs in patients with CPP.

Data collection

We collected patient data from hospital records and clinical interviews during follow-up visits. This included demographic information like height, age, and BMI. We also gathered further details on the usage of GnRH-a therapy, including reasons for noncompliance and therapy duration. The safety data was evaluated based on patient responses, covering symptoms such as pain or allergies at the injection site, premenstrual tension symptoms like vaginal bleeding, bone pain, and abdominal pain, as well as psychological symptoms such as mood swings and changes in appetite.

Statistical analysis

The dataset was simply analyzed using Microsoft Excel 2019.

RESULTS

Characteristics of patients

A total of 148 patients participated in the study. They were, on average, 11.56 years old with a standard deviation of 2.13 years. The age range was from 6 to 14 years. The patients had an average height of 142.85 cm, with a considerable deviation of 98.2 cm. Height measurements varied from 98.2 cm to 161.5 cm. The average BMI recorded was 19.92 with a standard deviation of 5.63, the max and min being 50.4 and 12.03, respectively. Treatment duration with GnRH-a therapy averaged 2.15 years, with a standard deviation of 1.39 years. The longest treatment period was 7 years, while the shortest one was 0.11 years (Table 1).

ADR noticed during GnRH-a therapy

The research study evaluated 148 patients receiving GnRH-a treatment. Of these, 28 patients did not report any adverse drug reactions (ADRs). Major ADRs most commonly reported by 75 patients included pain at the injection site and mood swings, also observed in 67 patients. Other noted ADRs from 53 patients encompassed weight gain and an increase in appetite, as mentioned by 44 patients, along with abdominal pain in 27 patients. 22 patients complained of bone pain, whereas allergic reactions, vaginal bleeding, and bruising were less common, reported by only 14, three, and four patients, respectively (Figure 1).

Compliance

Of the 148 cases studied, 93.9% (139 cases) adhered to the prescribed regimen. However, 6.1% (9 cases) did not comply. Six non-compliant cases were due to medication unavailability, two were due to inability to afford medication, and one was due to parental refusal.

DISCUSSION

This study aims to determine the long-term safety of GnRH-a treatment, drawing on data from patients with CPP who have received GnRH-a for a minimum of 6 months. Our research suggests that young children generally tolerate GnRH-a therapy well. The primary reported ADRs of GnRH-a include injection site pain, mood swings, and weight gain.

Several studies have corroborated our findings about these effects. One such study explored the long-term effects and considerable ADRs noted during GnRH-a treatment in patients with CPP. It revealed that local side effects like injection site pain are typically mild [12].

In addition, some studies addressed the issue of vaginal spotting or bleeding. One pointed out that a few female patients experienced vaginal spotting or bleeding after taking their first dose of GnRH-a, which is primarily related to a temporary rise in LH and FSH levels [12]. Following the use of GnRH-a, vaginal bleeding occurred in 28.5% of the cases (eight out of 28). Out of these, four girls had prolonged vaginal bleeding that lasted between 11 to 13 days. One girl had three recurring episodes during the second injection, and another experienced her fourth episode 6 months into the treatment course [13].

A study examined the medical records of 38 girls with CPP who underwent treatment with GnRH-a for a minimum of 18 months. The data indicated an increase in the BMI of these patients during the first year of therapy. The BMI increase was more substantial in girls with a baseline normal weight compared to those who were overweight, but the difference was not statistically significant [14].

Contrarily, a study yielded results that differed from ours, indicating that GnRH-a is less likely to increase the risk of overweight or obesity. This research compared two groups of girls based on their BMI. The data showed that girls who were administered the medication had lower BMI compared to those who were not. However, there was a minor initial increase in BMI levels at the onset of the GnRH-a treatment [1].

Our study has certain limitations, such as a small sample size and an inability to analyze long-term safety profiles.

CONCLUSION

Generally, treatment with GnRH-a is deemed safe and well tolerated, even though it does have numerous ADRs. However, no patients attribute their treatment to these effects. Nonetheless, some were unable to complete the treatment due to reasons such as high medication costs and limited availability. Thus, additional research is needed to evaluate the safety of GnRH-a treatment further.

REFERENCES

1. Luo X, Liang Y, Hou L, Wu W, Ying Y, Ye F. Long-term efficacy and safety of gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2021;94(5). doi:10.1111/cen.14410
2. Raju GAR, Chavan R, Deenadayal M, et al. Luteinizing hormone and follicle-stimulating hormone synergy: A review of role in controlled ovarian hyper-stimulation. J Hum Reprod Sci. 2013;6(4). doi:10.4103/0974-1208.126285
3. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol. 2016;4(3):265-274. doi:10.1016/S2213-8587(15)00380-0
4. Al Agha AE. Early Puberty and its Effect on Height in Young Saudi Females: A Cross-Sectional Study. Pediatrics & Therapeutics. 2015;05(01). doi:10.4172/2161-0665.1000233
5. Bouvattier C, Coste J, Rodrigue D, et al. Lack of effect of GnRH agonists on final height in girls with advanced puberty: A randomized long-term pilot study. Journal of Clinical Endocrinology and Metabolism. 1999;84(10). doi:10.1210/jcem.84.10.6032
6. Narayanan Namboothiri G, Chacko VI, Rashmi A, Sathyanath S, Anil M. Factors influencing age at menarche – A school based cross sectional study. Indian J Community Health. 2020;32(2). doi:10.47203/ijch.2020.v32i02.025
7. Wozniak M, Murias M. [Xenoestrogens: endocrine disrupting compounds]. Ginekol Pol. 2008;79(11):785-790.
8. Kim YJ, Kwon A, Jung MK, et al. Incidence and Prevalence of Central Precocious Puberty in Korea: An Epidemiologic Study Based on a National Database. J Pediatr. 2019;208:221-228. doi:10.1016/j.jpeds.2018.12.022
9. Ortmann O, Weiss JM, Diedrich K. Gonadotrophin-releasing hormone (GnRH) and GnRH agonists: mechanisms of action. Reprod Biomed Online. 2002;5 Suppl 1:1-7. doi:10.1016/s1472-6483(11)60210-1
10. Lee JW, Kim HJ, Choe YM, 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(3):135. doi:10.6065/apem.2014.19.3.135
11. Luo X, Hou L, Zhong Y, et al. An open label, multicenter clinical trial that investigated the efficacy and safety of leuprorelin treatment of central precocious puberty in Chinese children. Medicine (United States). 2021;100(51):E28158. doi:10.1097/MD.0000000000028158
12. De Sanctis V, Soliman AT, Di Maio S, Soliman N, Elsedfy H. Long-term effects and significant adverse drug reactions (ADRs) associated with the use of gonadotropin-

releasing hormone analogs (GnRHa) for central precocious puberty: A brief review of literature. Acta Biomedica. 2019;90(3):345-359. doi:10.23750/abm.v90i3.8736

13. Yeshaya A, Kauschansky A, Orvieto R, Varsano I, Nussinovitch M, Ben-Rafael Z. Prolonged vaginal bleeding during central precocious puberty therapy with a long-acting gonadotropin-releasing hormone agonist. Acta Obstet Gynecol Scand. 1998;77(3):327-329.

14. Lee SJ, Yang EM, Seo JY, Kim CJ. Effects of Gonadotropin-Releasing Hormone Agonist Therapy on Body Mass Index and Height in Girls with Central Precocious Puberty. Chonnam Med J. 2012;48(1):27. doi:10.4068/cmj.2012.48.1.27

Table 1. Demographics and baseline characteristic (n=148).

Age (Years)		**Max**	**Min**
Mean (SD)	**11.56 (2.13)**	**14**	**6**
Height (cm)			
Mean (SD)	**142.85 (15.51)**	**161.5**	**98.2**
BMI			
Mean (SD)	**19.92 (5.63)**	**50.4**	**12.03**
Duration of treatment (Years)			
Mean (SD)	**2.15 (1.39)**	**7**	**0.11**

Figure 1. Frequency distribution of ADR detected during GnRH-a therapy.