J Pediatr Res 2023;10(3):222-7
DOI: 10.4274/jpr.galenos.2023.48753

Original Article

Evaluation of Electrocardiographic Changes in Girls Receiving Gonadotropin-Releasing Hormone Analogs for Precocious Puberty

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ABSTRACT

Aim: Gonadotropin-releasing hormone analogs (GnRHa) are standard medical treatments for precocious puberty. Studies on their side effects in adults have shown that these drugs can cause changes in electrocardiography (ECG), along with some cardiovascular effects; however, the number of studies on children is limited. This study investigated the effects of these drugs on ECG parameters in children diagnosed with central precocious puberty (CPP).

Materials and Methods: This prospective study included 44 girls who were initiated GnRHa treatment and diagnosed with CPP. ECG was performed before treatment and repeated after 6 months of treatment.

Results: The mean age of the children was 9.13±1.55 years. Leuprolide acetate (3.75 mg IM) was administered to all of the patients following the standard protocol. A comparison of the pre-treatment and 6-month ECG parameters revealed a prolonged QT interval after treatment, with a statistically significant difference ($p<0.001$). There were no significant differences in the pre- and post-treatment values of PR, QRS, QT interval, QTc interval, QT dispersion, or QTc dispersion ($p>0.05$).

Conclusion: Despite a significant increase in QT interval on ECG with GnRHa compared to pre-treatment ECGs, this increase was attributed to a variability in heart rate. Even if regular ECG monitoring is considered after initiation of GnRHa treatment, they are believed to be safe drugs in children.

Keywords: ECG, GnRH agonist, precocious puberty, QT, QTc, QT dispersion, QTc dispersion

Introduction

Precocious puberty is defined as the onset of secondary sexual development before 8 years of age in girls and 9 years of age in boys, and its treatment depends on its underlying cause. Central precocious puberty (CPP) results from the premature maturation of the hypothalamic-pituitary-gonadal axis. It is characterized by sequential maturation of the breast bud and pelvic hair in girls and maturation of the testicles, penis, and pubic hair in boys. While CPP is idiopathic in 80-90% of girls, intracranial lesions are identified in 40-75% of boys with CPP (1,2). If necessary, the progression of puberty in CPP can be halted by administering gonadotropin-releasing hormone analogs (GnRHa). GnRHa acts by providing sustained stimulation to the pituitary gonadotropes rather than physiological

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Received: 14.08.2023 **Accepted:** 22.08.2023

pulsatile stimulation from hypothalamic GnRH. This results in the continuous stimulation of gonadotroph cells and leads to desensitization and suppression of gonadotropins. This results in a decrease in sex steroid production, which is called the suppression of the pituitary-gonadal axis (3). There are different pharmacological forms of GnRHa, including triptorelin, leuprolide, buserelin, nafarelin, and goserelin. In Turkey, only leuprolide is within the scope of reimbursement; therefore, this single agent is used for patients. There are two forms of leuprolid acetate: once every 4 weeks and once every 3 months (4).

The risk of GnRHa treatment causing a prolonged QT interval was reported during the treatment of men with prostate cancer, and it was suggested to be associated with changes in circulating testosterone concentrations (5). There have been no reports of prolonged QT intervals in women using GnRHa (6). In the current literature, the GnRHa reported to increase the risk of a prolonged QT interval are leuprolide and degarelix (7). However, it remains unclear whether this is a class effect and may indicate an increased risk for other GnRHas. Among the conditions treated with GnRHa in pediatrics, gender dysphoria in adolescent males is the clinical condition most similar to that in which the risk of prolonged QT interval with GnRHa has been reported (8). The number of pediatric studies in this field is limited.

This study aimed to evaluate the effects of GnRHa on electrocardiogram (ECG) parameters in girls diagnosed with precocious puberty.

Materials and Methods

This was a prospective study which included 44 girls who presented to the Adana City Training and Research Hospital, Clinic of Pediatric Endocrinology between April, 2020 and December, 2021, and who were initiated on the treatment of GnRH agonist with a diagnosis of CPP. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Adana City Training and Research Hospital (approval no: 1459, date: 17.06.2021). This study was initiated after obtaining written consent from all the participants and/or their families. The inclusion criteria were girls followed up with a diagnosis of idiopathic central precocious puberty and treatment with GnRHa (leuprolide acetate) 3.75 mg/28 days. In this tertiary center, 200 girls are diagnosed with CPP annually. The diagnosis was based on breast budding before 8 years of age, stimulated (LHRH test) LH level >5 IU/L, supported by bone age and pelvic ultrasonography. Serum LH and FSH concentrations were measured using an immunochemical assay, and dehydroepiandrosterone sulfate and T levels were measured using a radioimmunoassay (Ria) (Diagnostic Products Corporation, Los Angeles, CA, USA). Estradiol levels were measured using an immunoassay (Siemens Centaur XP).

The exclusion criteria were an existing congenital heart disease with hemodynamic effects, arrhythmia, the use of other drugs which can change ECG parameters, and abnormal admission ECG. A standard 12-lead ECG study was performed at 25 mm/s and 10 mm/mV, measured manually by a single pediatric cardiologist, and interpreted by a specialist. ECG was performed before treatment in patients whose diagnosis was confirmed after hormonal and biochemical evaluations. The ECG examination was repeated at 6 months of treatment in those patients who regularly used the treatment. While puberty examination and laboratory values were evaluated by the Department of Pediatric Endocrinology, the ECG parameters were determined blindly by the same pediatric cardiologist. Age at diagnosis, GnRHa (leuprolide acetate) administration, the prescribed dose, and any history of other diseases or medications were recorded on a pre-prepared form. This study was conducted in accordance with the principles of the Declaration of Helsinki.

The QT interval was measured from the beginning of the QRS complex to the end of the T wave on the ECG. QT dispersion was calculated by measuring the distance between the longest QT interval (QTmax) and the shortest QT interval (QTmin) on the ECG. The corrected QT interval as a function of heart rate was calculated using Bazett's formula ($QTc=QT/\sqrt{RR}$) and was defined as the corrected QT (QTc). QTc dispersion was measured by calculating the difference between the longest QTc (QTc max) and the shortest QTc (QTc min).

Statistical Analysis

The Statistical Package for the Social Sciences software (version 26.0) was used for the statistical analysis of the data. Categorical measurements are summarized as numbers and percentages, and continuous measurements as means and standard deviations (median, minimum-maximum, and Q1-Q3) where necessary. The Shapiro-Wilk test was used to determine whether the parameters in this study were normally distributed. A paired-sample t-test was used for normally distributed parameters and Wilcoxon signed-rank tests were used for non-normally distributed parameters. A multivariate linear regression model was used to determine the contribution of the independent variables to the variance of the dependent variable. The statistical significance level was set as 0.05.

Results

Forty-four girls with a mean age of 8.99±1.53 years were included in this study. The clinical characteristics of all the participants are summarized in Table I. All patients were initiated on an intramuscular injection of leuprolide acetate 3.75 mg/28 days as GnRHa. The mean GnRHa was 112.9±33.0 µg/kg.

The comparison of the pre-treatment and 6-month ECG parameters of the patients revealed a prolonged QT interval and a lower pulse rate (beats/minute) after treatment, with a statistically significant difference (p<0.001, p<0.001). There were no significant differences in the pre- and post-treatment values of PR, QRS, QTc interval, QT dispersion, or QTc dispersion (Table II). There was a significant decrease in the heart rate on 6 months ECG.

As shown in Table III, multivariate linear regression analysis was performed to determine the correlation between the ECG parameters and GnRHa dose (µg/kg). A significant negative correlation was observed between GnRHa dose and PR interval (p=0.049), whereas no significant correlation was found between GnRHa dose and QRS, QT mean, QT dispersion, QTc, or QTc dispersion (Table III). Boxplot diagrams of the pre- and post-GnRHa treatment OTc intervals are shown in Figure 1.

Table I. Clinical and laboratory characteristics of patients

Characteristics	Mean ± SD	Min.-Max.	Q1	Med	Q3
Age at diagnosis (years)	8.99-1.53	0.82-10.85	8.39	9.24	9.89
Weight SDS	0.96±1.18	-1.94-3.21	0.28	1.06	1.81
Height SDS	0.58±1.20	-2.11-3.69	0.10	0.59	1.11
BMI SDS	0.80-1.01	-1.20-3.21	-0.005	0.93	1.37
LH (mIU/mL)	2.04-1.85	0.0-7.61	0.63	1.54	3.04
FSH (mIU/mL)	5.11-2.05	1.0-10.0	3.23	5.18	6.21
Estrodiol (pg/ml)	30.92-19.99	0-0.97	18.5	28.0	45.5
GnRHa dose (mg)	3.80-0.60	2.50-7.50	3.75	3.75	3.75
GnRHa dose (µg/kg)	112.9-33.0	64.66-227.27	91.8	104.45	118.3

Continuous variables are expressed as mean ± standard deviations
Q1, Q3: 1st and 3rd quartile, Med: Median, SDS: Standard deviation scores, BMI: Body mass index, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, GnRH: Gonadotropin-releasing hormone, Min.-Max.: Minimum-Maximum

Table II. Comparison of pre- and post-GnRHa treatment ECG parameters

Parameters		Mean ± SD	Q1	Med	Q3	p-value
Heart rate (beats/minute)	**Pre-treatment**	95.3±16.6	83.3	94	104	**<0.001**‡,**
	Post-treatment	84.5±16.3	71.3	83	92.5	
PR (ms)	**Pre-treatment**	121.9±13.8	114	120	128	0.643‡
	Post-treatment	120.5±15.5	110.5	119	133.5	
QRS (ms)	**Pre-treatment**	74.8±7.3	70.0	74	79.5	0.246‡
	Post-treatment	76.5±12.5	70.5	75	80	
QT min (ms)	**Pre-treatment**	297.1±25.1	280	290	320	**<0.001**‡,**
	Post-treatment	311.2±27.3	296	320	325.5	
QT max (ms)	**Pre-treatment**	317.7±26.3	297	320	337.5	**<0.001**†,**
	Post-treatment	336.3±29.8	320	340	360	
QT mean (ms)	**Pre-treatment**	307.4±25.2	288.5	304.5	325	**<0.001**†,**
	Post-treatment	323.8±27.8	308.5	324	341.5	
QT dispersion (ms)	**Pre-treatment**	20.5±9.9	12	20	30	0.071‡
	Post-treatment	25.0±13.6	17	20	40	

Table II. Continued						
Parameters		**Mean ± SD**	**Q1**	**Med**	**Q3**	**p-value**
QTc min (ms)	**Pre-treatment**	374.2±22.7	358.8	374.5	387	0.074†
	Post-treatment	366.5±18.1	354	367	375.8	
QTc max (ms)	**Pre-treatment**	399.9±21.3	384.3	400.5	416	0.651†
	Post-treatment	398.3±18.8	385.5	400	413	
QTc mean (ms)	**Pre-treatment**	387.1±20.4	372.5	386.25	401.5	0.187†,**
	Post-treatment	382.38±16.54	368.5	381.3	395.5	
QTc dispersion (ms)	**Pre-treatment**	25.8±16.4	11.25	22.5	36	0.148‡
	Post-treatment	31.7±16.5	21	31.0	42	

*p<0.05, **p<0.001, †Paired-sample t-test, ‡Wilcoxon signed ranks test
Q1, Q3: 1st and 3rd quartile, Med: Median, SD: Standard deviation, GnRHa: Gonadotropin-releasing hormone analogs, ECG: Electrocardiography

Table III. Multivariate linear regression model analysis results between ECG parameters and GnRHa dose (µg/kg)			
Parameters	**β**	**(95% CI)**	**p-value**
PR (ms)	-0.690	-1.378- -0.003	0.049*
QRS (ms)	-1.217	-2.654- 0.220	0.094
QT mean (ms)	-0.222	-.0727- 0.283	0.378
QT dispersion (ms)	-0.144	-1.228- 0.940	0.789
QTc mean (ms)	-0.344	-0.873- 0.185	0.195
QTc dispersion (ms)	0.133	-0.548- 0.814	0.694

A p-value <0.05 is considered statistically significant
ms: Milliseconds, CI: Confidence interval, GnRHa: Gonadotropin-releasing hormone analogs, ECG: Electrocardiography

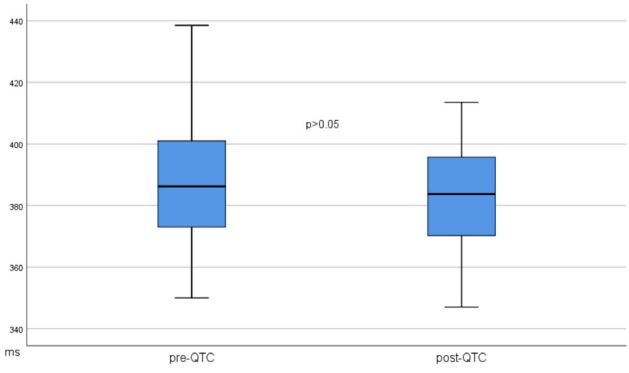

Figure 1. Boxplot diagram of pre- and post-GnRHa treatment QTc intervals
p>0.05 (paired Student's t-test). Abbreviations: ms, milliseconds; pre-QTC, pre-treatment values of QTc intervals; post-QTC, pre-treatment values of QTc intervals.

Discussion

Precocious puberty leads to premature closure of the epiphyseal disks and short stature in adulthood and therefore has important social consequences (9,10). GnRH agonists are preferred for the treatment of CPP. This study prospectively evaluated the effects of this treatment on ECG parameters in girls diagnosed with CPP who were treated with GnRHa. Administration of GnRH agonists (leuprolide acetate) had a statistically significant effect on QT intervals but had no significant effect on PR, QRS, QT, QTc intervals, QT dispersion, or QTc dispersion. However, the pre- and post-treatment values of each participant were within the normal range, according to the reference ECG parameters for age (11).

GnRH agonists and QT interval prolongation have been carefully studied in prostate cancer studies (5). There have been no reports of prolonged QT intervals in women using GnRHa. A prolonged QT interval increases the risk of developing torsades de pointes, which is a ventricular arrhythmia which can lead to sudden cardiac death (12). In addition, studies have shown that ventricular repolarization parameters QT, QTc interval, and QT dispersion can predict ventricular arrhythmia events and death. The list of drugs known to cause a prolonged QT interval is regularly updated (13,14). Currently, the GnRHas with a reported increase in the risk of prolonged QT interval are leuprolide and degarelix (15,16). A study by Gagliano-Jucá et al. (14) compared one group using leuprolide acetate treatment for androgen suppression in prostate cancer and another group not using

this treatment and they found a statistically significantly prolonged QTc interval in the group receiving treatment. In our study, all parameters indicative of ventricular repolarization were evaluated, and no difference was found in the QTc interval with leuprolide acetate administration; however, the results showed a statistically significant increase in the QT interval. This may have been caused by a statistically significant change in pre- and post-treatment heart rates.

In Smith et al.'s (16) study of the cardiovascular safety of degarelix treatment in prostate cancer, the results were similar to those of the group receiving leuprolide treatment. In contrast, another study evaluating the effect of degarelix treatment and a placebo on cardiac polarization in a prostate cancer group reported that degarelix treatment was safe even at high doses (17). In our study, linear regression was performed to evaluate the correlation between leuprolide acetate doses (μg/kg) and ECG parameters, which revealed that increasing therapeutic doses did not significantly increase PR, QRS, or QT intervals.

Among the conditions treated with GnRHa in childhood, gender dysphoria is the clinical condition most similar to those in which the risk of a prolonged QT interval has been described. The testosterone levels in these patients were suppressed by GnRHa administration. A retrospective study examining the ECG parameters of 33 adolescents (19 assigned males, 14 assigned females) who used leuprolide acetate for puberty suppression due to gender dysphoria found no QTc prolongation in any young people (18). Although the number of pediatric studies in this field is limited, the Drug and Therapeutics Committee has made the following recommendations for individuals receiving GnRHa treatment: A screening ECG is recommended if the patient is taking other drugs known to cause a prolonged QT interval; has a history of congenital heart disease, arrhythmia, or long QT syndrome; has a family history of long QT syndrome or sudden cardiac death; or has symptoms associated with long QT syndrome, including syncope. After ECG screening, the ECG should be repeated when the GnRHa dose reaches a steady state. If the patient has long QT syndrome with prolonged QTc or other ECG abnormalities, a family history of long QT syndrome, or sudden death, the patient should be referred to cardiology. Healthcare professionals should counsel patients about arrhythmia symptoms, including palpitations and syncope. Healthcare professionals should continue to receive information regarding new drugs while continuing GnRHa treatment (17). Therefore, regular ECG monitoring should be considered after treatment initiation in patients treated with GnRH agonists.

Study Limitations

The limitations of this study were its single-center design, small sample size, and the lack of a control group. In addition, only 6-month post-treatment ECG data were available.

Conclusion

The results of this study showed that there were no significant changes in the parameters studied, including QRS, QTc, QT dispersion, and QTc dispersion, after the use of GnRH agonists. Evaluation of the correlation between GnRH agonist dosege (μg/kg) and ECG parameters revealed that it did not significantly increase QRS, QT dispersion, or QTc dispersion at increasing therapeutic doses. Even if regular ECG monitoring is considered after the initiation of GnRHa treatment, they are believed to be safe drugs in children, as there is not enough evidence to contradict this yet.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Adana City Training and Research Hospital (approval no: 1459, date: 17.06.2021).

Informed Consent: This study was initiated after obtaining written consent from all the participants and/or their families.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., A.O., Concept: E.E., Design: E.E., A.O., Data Collection or Processing: E.E., E.E., Analysis or Interpretation: E.E., Literature Search: E.E., A.A., Writing: E.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study received no financial support.

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