ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2024.2024-2-8

J Clin Res Pediatr Endocrinol 2024;16(4):426-430

Electrocardiographic Findings in Children Treated with Leuprolide Acetate for Precocious Puberty: Does it Cause Prolonged QT?

Esma Ebru Altun, Ayşe Yaşar, Fatma Dursun, Gülcan Seymen, Heves Kırmızıbekmez

University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Pediatric Endocrinology, İstanbul, Turkey

What is already known on this topic?

Gonadotropin releasing hormone (GnRH) analogues are the only drugs used in the treatment of central precocious puberty (CPP) in children. Increased cardiovascular events and especially a serious disorder of prolonged QT in some adult patient groups while receiving GnRH analogue treatment have been reported in recent studies. Prolonged QT and arrhythmias are life-threatening conditions and can be detected by electrocardiogram (ECG), which is a cheap, non-invasive, and easily accessible test. However, more evidence-based information is needed to recommend ECG before and during GnRH analogue treatment in children.

What this study adds?

In this study, no prolonged QT or other pathological electrophysiological findings were found in young girls, aged 5-11 years, receiving leuprolide acetate treatment due to CPP. No correlation was found between corrected QT values and age, treatment duration, total cumulative dose, and anthropometric data in this cohort. These results suggested no adverse effect of leuprolide acetate on cardiovascular adverse events.

Abstract

Objective: Central precocious puberty (CPP) is treated with long-acting gonadotropin releasing hormone (GnRH) analogues (GnRHa). Some adult patients undergoing GnRHa treatment experienced prolonged QT syndrome, which is associated with an increased risk of serious cardiac events, such as myocardial infarction, stroke, arrhythmias, and sudden cardiac death.

Methods: Seventy-four patients, aged between 5 and 11 years and diagnosed with CPP but with no other concomitant disease or medication use, underwent electrocardiogram (ECG) assessment. They had been receiving 3.75 mg leuprolide acetate (Lucrin® Depot) injections every 28 days for at least three months.

Results: The ECGs of all patients showed a corrected QT (QTc) interval within normal limits, consistent with the data for healthy Turkish children of the same age and gender. No other pathological physical examination or ECG findings were observed. Furthermore, there was no significant difference in QTc interval when adjusted for age, anthropometric data, or the duration or cumulative dose of the treatment.

Conclusion: The study found no correlation between QTc interval values and age, treatment duration, total cumulative dose, and anthropometric data. These findings suggest that cardiovascular adverse events associated with GnRHa treatment may be related to age and other underlying physiopathological conditions in adults rather than being directly due to the drug.

Keywords: Precocious puberty, leuprolide acetate, children, ECG, prolonged QT

Cite this article as: Altun EE, Yaşar A, Dursun F, Seymen G, Kırmızıbekmez H. Electrocardiographic Findings in Children Treated with Leuprolide Acetate for Precocious Puberty: Does it Cause Prolonged QT? J Clin Res Pediatr Endocrinol. 2024;16(4):426-430

Address for Correspondence: Heves Kırmızıbekmez MD, University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Pediatric Endocrinology, İstanbul, Turkey
E-mail: heveskirmizibekmez@yahoo.com **ORCID:** orcid.org/0000-0002-8663-3452

Conflict of interest: None declared
Received: 17.02.2024
Accepted: 09.05.2024
Epub: 15.05.2024
Publication date: 04.12.2024

Introduction

Central precocious puberty (CPP) is the premature development of secondary sexual characteristics in girls before the age of 8 years and in boys before the age of 9 years due to the early maturation of the hypothalamic-pituitary-gonadal axis (1). The treatment of CPP involves the use of long-acting gonadotropin releasing hormone (GnRH) analogues (GnRHas), which paradoxically downregulate and subsequently suppress the HPG axis. These drugs have been used for many years (2). The aim of treatment for CPP is to preserve height potential, prevent early menarche, and address psychosocial issues. GnRH agonists are commonly used in the treatment of conditions such as prostate and breast cancer, endometriosis, and uterine fibroids in adults. It has been reported that adult patients undergoing GnRHa treatment may develop prolonged QT syndrome, which is linked to a higher risk of serious cardiac events, including myocardial infarction, stroke, arrhythmias, and sudden cardiac death. The elevated incidence of cardiovascular events in adult male patients undergoing androgen deprivation therapy for prostate cancer has been mainly attributed to the androgen deprivation. However, GnRH agonists have been found to be more strongly linked to cardiovascular events than other agents, such as GnRH antagonists, used for androgen deprivation. It has been suggested that GnRH agonists have a more significant impact on cardiovascular events beyond androgen deficiency (3,4,5,6).

The drug's prospectus reports these complications, but there is no evidence in the literature regarding their effects on women and children. Thus, the aim of this study was to investigate the effect of leuprolide acetate treatment on electrocardiogram (ECG) findings in children with CPP. Investigating the effects of this treatment on cardiac rhythm and corrected QT (QTc) interval is important to assess the safety of this drug in the pediatric population.

Methods

Girls aged between 5 and 11 years and diagnosed with CPP, were included in this prospective cross-sectional study. The study received approval from Ümraniye Training and Research Hospital Local Ethics Committee (approval number: B.10.1.TKH.4.34.H.GP.0.01/160, date: 15.05.2023). The authors have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

The decision for treatment was typically made on an individual basis, considering the patient's age at puberty onset, rate of progression of puberty, accelerated growth and bone age, hormone levels, ultrasonographic measurements, and the expectation of early menarche. The study included patients who had been receiving 3.75 mg leuprorelin acetate (Lucrin® Depot) injections every 28 days for at least three months. The birth weight, week of gestation at birth, nutritional status, and history of any previous or ongoing disease medication use were recorded. The study included patients who only used leuprolide acetate as GnRHa therapy and were still under treatment during the study period. Among these patients, patients who had any health problems other than early puberty, who used any other medications within the last three months (therapy for allergic diseases, attention disorders, epilepsy, psychopathologies, inflammatory diseases), and who did not agree to have an ECG at the baseline study visit were excluded. A repeat ECG was requested if it was not of sufficient quality due to artifacts, but those who did not have a repeat ECG were also excluded from the study.

All patients underwent a thorough physical examination, with particular attention paid to the cardiovascular system, and an ECG test at their first visit after being enrolled in the study. During this visit, the following parameters were recorded: age, duration of treatment (in months), cumulative dose of leuprolide acetate (calculated as total mg/kg), height, weight, and body mass index. Anthropometric data were recorded as standard deviation (SD) scores which were calculated using an online application (Child Metrics®) which uses reference data for Turkish children (7,8). The ECG results were evaluated by a pediatric cardiologist. The cardiac rhythm, heart rate, and QTc interval, calculated using the Bazett formula, were recorded (9). The primary focus of ECG analysis was the QTc interval, which is key for assessing the cardiac repolarization phase and potential arrhythmia risk (10). Correlation analyses were used to investigate potential relationships between the variables and ECG measurements. The QTc intervals of the patients were compared to the reference values of age- and gender-matched healthy Turkish children. The reference value for 5-8 year-old girls is 422 (382-465) milliseconds (ms) and for 8-12 year-old girls is 422 (377-486) ms (11).

Statistical Analysis

Statistical analysis was conducted using IBM Statistical Package for the Social Sciences, version 22 (IBM Inc., Armonk, NY, USA). The normality of the data was evaluated using the Shapiro-Wilk test. The results are presented as mean ± SD since the data was normally distributed. The independent-samples t-test was used to compare the independent groups. The Wilcoxon signed test was used to compare related samples. For correlation analyses, the

Pearson test was used for normally distributed variables. The level of significance for all analyses was set at $p < 0.05$.

Results

The study analyzed a cohort of 74 female patients, aged between 5 and 11 years, who were receiving leuprolide acetate. The mean age at the start of treatment was 7.58 ± 0.91, ranging 5.2-9.5 years, and the mean age at which an ECG was performed was 8.95 ± 1.17 years, ranging 5.5-11.0 years. The mean total duration of treatment before the ECG was 17.6 ± 10.5 months, with a minimum of 3 months and a maximum of 66 months, and the cumulative dose received was 58.4 ± 31.3 mg/m^2, ranging 10.04-186.7 mg/m^2.

The cardiology assessment showed no symptoms or pathological physical examination findings. Two patients had nonspecific ST-T changes. Among the 72 patients with normal ECG findings, 37 had respiratory sinus arrhythmia and two had only one atrial escape beat. The QTc interval was within normal limits in all ECGs. The mean QTc was 390 ± 10 ms, ranging from 360-430 ms, which is within normal limits and was not longer than the reference value for healthy Turkish children according to age and gender. Non-parametric tests revealed no difference between QT intervals before treatment and at the end of sixth month of the treatment in seven patients who were newly diagnosed during the study ($p = 0.753$). There was no significant difference between patients who received leuprolide acetate treatment for 18 months or more and those who received it for a shorter period. In addition, there was no significant difference between patients who received a leuprolide acetate cumulative dose of 2 mg/kg or more and those who received less (Table 1). Our analysis did not reveal any correlation between the QTc values and the patients' age, duration of treatment, cumulative dose, or anthropometric data, as shown in Table 2.

Discussion

This study evaluated ECG findings in young girls, aged 5-11 years, who were receiving leuprolide acetate treatment for CPP. No prolonged QT or other pathological electrophysiological findings were observed in any of the 74 patients. The absence of correlation between QTc values and age, treatment duration, total cumulative dose, and anthropometric data in our patients suggests that the adverse cardiovascular events previously reported in adults may be due to different underlying pathological mechanisms rather than any direct effect of the drug.

Recent reports have highlighted an increased risk of cardiovascular events, including prolonged QT syndrome, in some adult patients receiving GnRHa treatment. This has raised concerns about the safety of GnRHas, which are the only treatment agents used for CPP in children. Prolonged QT and arrhythmias may be detected by ECG, a cheap,

Table 1. The comparison of QTc intervals of patients on leuprolide acetate between short- and long-term users, and between higher- and lower-dose users

Duration of treatment			
	≥18 months (n = 37)	**< 18 months (n = 37)**	**p**
QTc interval (ms)	393 ± 18	395 ± 21	0.716
Cumulative dose of the GnRHa			
	≥2 mg/kg (n = 35)	**< 2 mg/kg (n = 39)**	**p**
QTc interval (ms)	391 ± 18	397 ± 21	0.200

QTc: corrected QT, GnRHa: gonadotropin releasing hormone analogues

Table 2. Correlations of treatment parameters and anthropometric measurements with corrected QT interval

QTc interval		
	r	**p**
Age	-0.064	0.602
Duration of treatment (months)	-0.090	0.463
Cumulative dose (mg/kg)	-0.068	0.577
Cumulative dose (mg/m^2)	-0.080	0.515
Weight SDS	-0.050	0.684
Height SDS	0.001	0.997
BMI SDS	-0.057	0.641

QTc: corrected QT, BMI: body mass index, SDS: standard deviation score

non-invasive, and easily accessible test. However, more information should be provided before recommending ECGs before and during GnRHa treatment in children.

Acquired prolonged QT syndrome can be caused by several major classes of drugs, with new ones continuing to be identified. A study from the United States reported antiarrhythmic drugs were responsible for 77% of cases (12). Other medications associated with prolonged QT include psychotropic drugs, gastrointestinal medications, antimicrobials, and tyrosine kinase inhibitors. Antimicrobial medications that prolong QT include macrolide antibiotics, fluoroquinolone antibiotics, and antifungal drugs (13). It has been reported that erythromycin led to a two-fold increase in risk of sudden cardiac death compared to nonusers (14). Painkillers (non-steroidal anti-inflammatory drugs, opioids, anticonvulsants, antidepressants, cannabinoids, and muscle relaxants), proton pump inhibitors, antiemetics, and diuretics are also reported to be causes of prolonged QT (15,16).

Antiarrhythmic drugs are used for cardiological indications and are followed by repeated ECGs under the supervision of a cardiologist. However, antimicrobial treatments, painkillers, and proton pump inhibitors are used without such precautions. Furthermore, there is no recommendation for cardiological evaluation before starting or during follow-up for GnRHas.

Waldner et al. (17) recently reported a study of 33 gender-diverse young people who were initiated on leuprolide acetate. The mean age of the cohort was 13.7 ± 2.1 years, and the mean post-leuprolide acetate QTc was 415 ± 27 ms (range 372-455). Only 24.2% of the patients had a borderline QTc (440-460 ms), and none had a prolonged QTc despite concomitant medications in twenty-two (66.7%).

The Pediatric Endocrine Society has issued guidelines regarding the potential risk of GnRHas. It is recommended to perform a screening ECG for patients who are on a medication known to cause QTc prolongation, have a personal history of congenital heart disease, arrhythmia, or long QT syndrome, have a family history of long QT syndrome or sudden cardiac death, and for those who experience symptoms of long QT syndrome, including syncope. It is recommended to perform a repeat ECG when the GnRHa dose has reached steady state in these groups. Patients should also be counseled about symptoms of arrhythmia, including palpitations and syncope. The authors conclude that further studies are necessary to investigate the risk of prolonged QT with GnRHa therapy in children and young adults (18).

Study Limitations

This was a single center study conducted in a limited number of patients. This was because of the exclusion of patients having any additional disease in addition to CCP or were on medications in addition to leuprolide acetate. The main limitation was the small number of patients who were newly diagnosed and underwent ECG before the treatment was started.

Conclusion

The results of this study showed no prolonged QT or any other ECG abnormality with short- or long-term exposure to GnRHa treatment, leuprolide acetate, in young girls with CPP.

Ethics

Ethics Committee Approval: Ethics approval to conduct this study was obtained from the Medical Ethics Committee of the University of Oldenburg (no: 2021-024, date: 11.02.2021).

Informed Consent: Retrospective study.

Acknowledgement

We would like to thank Dr. Yunus Emre Sarı and Prof. Dr. Taliha Öner from the Pediatric Cardiology Clinic for their help in evaluating the electrocardiogram results in this study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Esma Ebru Altun, Ayşe Yaşar, Fatma Dursun, Gülcan Seymen, Heves Kırmızıbekmez, Concept: Esma Ebru Altun, Heves Kırmızıbekmez, Design: Esma Ebru Altun, Heves Kırmızıbekmez, Data Collection or Processing: Esma Ebru Altun, Ayşe Yaşar, Fatma Dursun, Gülcan Seymen, Heves Kırmızıbekmez, Analysis or Interpretation: Esma Ebru Altun, Ayşe Yaşar, Heves Kırmızıbekmez, Literature Search: Esma Ebru Altun, Ayşe Yaşar, Fatma Dursun, Gülcan Seymen, Heves Kırmızıbekmez, Writing: Esma Ebru Altun, Heves Kırmızıbekmez.

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

References

1. Cheuiche AV, da Silveira LG, de Paula LCP, Lucena IRS, Silveiro SP. Diagnosis and management of precocious sexual maturation: an updated review. Eur J Pediatr. 2021;180:3073-3087. Epub 2021 Mar 21
2. Eugster EA. Treatment of Central Precocious Puberty. J Endocr Soc. 2019;3:965-972.

3. Abbasi D, Faiek S, Shetty S, Khan E. Shock From Twisting Peaks: A Rare Case of Recurrent Torsades de Pointes Secondary to Leuprolide-Induced Prolonged QT. Cureus. 2020;12:e9041.
4. Kim J, Freeman K, Ayala A, Mullen M, Sun Z, Rhee JW. Cardiovascular Impact of Androgen Deprivation Therapy: from Basic Biology to Clinical Practice. Curr Oncol Rep. 2023;25:965-977. Epub 2023 Jun 5
5. Olsson H, Petri N, Erichsen L, Malmberg A, Grundemar L. Effect of Degarelix, a Gonadotropin-Releasing Hormone Receptor Antagonist for the Treatment of Prostate Cancer, on Cardiac Repolarisation in a Randomised, Placebo and Active Comparator Controlled Thorough QT/QTc Trial in Healthy Men. Clin Drug Investig. 2017;37:873-879.
6. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol. 2014;65:565-573. Epub 2013 Nov 1
7. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015;7:280-293.
8. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol. 2017;9:182-184. Epub 2017 Apr 26
9. Dahlberg P, Diamant UB, Gilljam T, Rydberg A, Bergfeldt L. QT correction using Bazett's formula remains preferable in long QT syndrome type 1 and 2. Ann Noninvasive Electrocardiol. 2021;26:e12804. Epub 2020 Oct 18
10. Lester RM, Paglialunga S, Johnson IA. QT Assessment in Early Drug Development: The Long and the Short of It. Int J Mol Sci. 2019;20:1324.
11. Semizel E, Oztürk B, Bostan OM, Cil E, Ediz B. The effect of age and gender on the electrocardiogram in children. Cardiol Young. 2008;18:26-40. Epub 2007 Dec 20
12. Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan PC, Hohnloser SH, Shimizu W, Schwartz PJ, Stanton M, Murray KT, Norris K, George AL Jr, Roden DM. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation. 2002;105:1943-1948.
13. Charles I Berul. Acquired long QT syndrome: Definitions, pathophysiology, and causes. Up To date (ed. Samuel Asirvatham); last updated Sep 21, 2022.
14. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med. 2004;351:1089-1096.
15. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. ScientificWorldJournal. 2012;2012:212178. Epub 2012 Apr 19
16. Klivinyi C, Bornemann-Cimenti H. Pain medication and long QT syndrome. Korean J Pain. 2018;31:3-9. Epub 2018 Jan 2
17. Waldner RC, Doulla M, Atallah J, Rathwell S, Grimbly C. Leuprolide Acetate and QTc Interval in Gender-Diverse Youth. Transgend Health. 2023;8:84-88.
18. Miller BS, Kamjob M; on behalf of the Drug and Therapeutics Committee. Risk of Prolonged QT Interval with Gonadotropin Releasing Hormone Agonists. Mclean, VA: Pediatric Endocrine Society, 2017.