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

Research Article

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

Altun EE et al. Electrocardiographic Findings in Children Treated with Leuprolide Acetate

Esma Ebru Altun, Ayşe Yaşar, Fatma Dursun, Gülcan Seymen, Heves Kırmızıbekmez
University of Health Sciences, Ümraniye Training and Research Hospital, Department of Pediatric Endocrinology, Istanbul

What is already known?
GnRH analogues are the only treatment agents used in the treatment of central precocious puberty in children. Increased cardiovascular events and especially a serious disorder 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 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, 5-11 years of age, under leuprolide acetate treatment due to central precocious puberty. No correlation was found between QTc values and age, treatment duration, total cumulative dose, and anthropometric data in our patients. Our results suggested no adverse effect of leuprolide acetate on cardiovascular adverse events.

Abstract
Introduction: Central precocious puberty is treated with long-acting GnRH analogues. 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.
Method: Seventy-four patients, aged between 5 and 11 years and diagnosed with central precocious puberty but with no other concomitant disease or medication use, underwent electrocardiogram assessment**.** They had been receiving 3.75 mg leuprolide acetate (Lucrin® Depot) injections every 28 days for at least three months.
Results: The electrocardiograms of all patients showed a QTc interval within normal limits, consistent with the data of 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 in relation to 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. The findings suggest that cardiovascular adverse events associated with GnRHa may be related to age and other underlying physiopathological conditions rather than the drug.
Keywords: Precocious puberty, leuprolide acetate, children, ECG, prolonged QT

Heves Kırmızıbekmez MD, University of Health Sciences, Ümraniye Training and Research Hospital, Department of Pediatric Endocrinology, Istanbul
+90 216 650 76 76
Heveskirmizibekmez@yahoo.com
17.02.2024
09.05.2024
0000-0002-8663-3452

Published: 03.06.2024

Introduction
Central precocious puberty (CPP) is the premature development of secondary sexual characteristics in girls before the age of 8 and in boys before the age of 9 due to the early maturation of the hypothalamic-pituitary-gonadal axis (1). The treatment of CPP involves the use of long-acting 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. Gonadotropin-releasing hormone 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 such as 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 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 (3-6).
The drug's prospectus reports these complications, but there is no evidence in the literature regarding their effects on women and children.
The aim of this study was to investigate the effect of leuprolide acetate treatment on electrocardiographic (ECG) findings in children with CPP, as there is currently insufficient information on this issue. Investigating the effects of this treatment on cardiac rhythm and corrected QT interval is crucial to determine its safety in the pediatric population.
Methods
Seventy-four patients aged between 5 and 11, diagnosed with central precocious puberty, were included in this prospective cross-sectional study. The study received approval from our hospital's 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, progression rate 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, nutritional status, history of any previous or ongoing disease medication use were questioned by the researchers. The study included patients who only have used leuprolide acetate as GnRH analogue therapy and are 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 control visit were excluded. A repeat ECG was requested if it was not of sufficient quality due to artifacts, but those who did not have them repeated 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 (BMI). Anthropometric data were recorded as standard deviation scores (SDS) which were calculated using an online application (Child Metrics®) which takes references for Turkish children (7-8). The ECG results were evaluated by a pediatric cardiologist. The cardiac rhythm, heart rate, and corrected QT (QTc) interval, calculated using the Bazett formula, were recorded (9). The primary focus of ECG analysis was the QTc interval, which is crucial for assessing the cardiac repolarization phase and potential arrhythmia risk. Correlation analyses were used to investigate potential relationships between the variables and electrocardiographic 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 milliseconds (ms) (382-465), while for 8-12-year-old girls it is 422 ms (377-486) (11).

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics 22 (IBM SPSS, Türkiye). First, the normality of the data was evaluated using the Shapiro-Wilk test. The results were 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 (range: 5.2-9.5 years), and the mean age at which an electrocardiogram (ECG) was performed was 8.95±1.17 years (range: 5.5-11.0 years.) The total duration of treatment before the ECG was 17.6±10.5 months (range: 3-66 months), and the cumulative dose received was 58.4±31.3 mg/m^2/day (range: 0.32-5.64 mg/m^2/day).

The cardiologic assessment showed no symptoms or pathologic 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 electrocardiograms. The mean QTc was 390±10 ms (range: 360-430 ms), which is within normal limits and not longer than the reference value of healthy Turkish children according to age and gender. Non-parametric tests revealed no difference between baseline and under-treatment QT intervals 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. Additionally, 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 (refer to 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 under leuprolide acetate treatment due to CPP. No prolonged QT or other pathological electrophysiological findings were observed. The absence of correlation between QTc values and age, treatment duration, total cumulative dose, and anthropometric data in our patients suggests that the cardiovascular adverse events previously reported in adults may be due to different underlying pathological mechanisms rather than the 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 central precocious puberty in children. Prolonged QT and arrhythmias are life-threatening conditions that can be detected by ECG, a cheap, non-invasive, and easily accessible test. However, it is necessary to provide more information on recommending ECGs before and during treatment in children.

Acquired prolonged QT syndrome can be caused by several major classes of drugs, with new ones continuing to be identified. According to a study from the United States, 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). According to a report, users of erythromycin had a twofold increased risk of sudden cardiac death compared to nonusers (14). Painkillers (NSAIDs, opioids, anticonvulsants, antidepressants, cannabinoids, and muscle relaxants), proton pump inhibitors, antiemetics, and diuretics are also reported as causes of prolong QT (15, 16). Antiarrhythmic drugs are used for cardiological indications and are followed by repeated electrocardiograms (ECGs) under the supervision of a cardiologist. However, antimicrobial treatments, painkillers, and proton pump inhibitors are used without precaution. Furthermore, there is no recommendation for cardiological evaluation before starting or during follow-up for GnRHas

Waldner et al. recently reported a study on thirty-three gender-diverse youth 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 of the 33 youth on leuprolide acetate had a prolonged QTc despite concomitant medications in twenty-two (66.7%) (17).

The Pediatric Endocrine Society has issued guidelines regarding the potential risk of GnRHas. It is recommended to perform a screening electrocardiograph (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 electrocardiogram (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 is a single center study conducted on a limited number of patients due to exclusion of patients having any additional disease or medications other than precocious puberty. The main limitation of our study 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 another electrocardiographic abnormality with short- and long-term exposure to GnRHa treatment in young children with precocious puberty.

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 ECG results in this study.

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(10):3073-3087. doi:10.1007/s00431-021-04022-1).
2. Eugster EA. Treatment of Central Precocious Puberty. J Endocr Soc. 2019;3(5):965-972. Published 2019 Mar 28. doi:10.1210/js.2019-00036
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(7):e9041. Published 2020 Jul 7. doi:10.7759/cureus.9041
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(9):965-977. doi:10.1007/s11912-023-01424-2.
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(9):873-879. doi:10.1007/s40261-017-0547-7
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(3):565-573. doi:10.1016/j.eururo.2013.10.032
7. Neyzi O, Bundak R, Gökçay G, et al. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015;7(4):280-293. doi:10.4274/jcrpe.2183,
8. Demir, K., Özen, S., Konakçı, E., Aydın, M., & Darendeliler, F. A comprehensive online calculator for pediatric endocrinologists: ÇEDD Çözüm/TPEDS metrics. Journal of Clinical Research in Pediatric Endocrinology 2017; 9: 182-184.
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(1):e12804. doi:10.1111/anec.12804
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(6):1324. Published 2019 Mar 15. doi:10.3390/ijms20061324
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(1):26-40. doi:10.1017/S1047951107001722
12. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation. 2002;105(16):1943-1948. doi:10.1161/01.cir.0000014448.19052.4c].
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(11):1089-1096. doi:10.1056/NEJMoa040582].
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. doi:10.1100/2012/212178
16. Klivinyi C, Bornemann-Cimenti H. Pain medication and long QT syndrome. Korean J Pain. 2018;31(1):3-9. doi:10.3344/kjp.2018.31.1.3
17. Waldner RC, Doulla M, Atallah J, Rathwell S, Grimbly C. Leuprolide Acetate and QTc Interval in Gender-Diverse Youth. Transgend Health. 2023;8(1):84-88. Published 2023 Feb 8. doi:10.1089/trgh.2021.0102
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.

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			
QTc interval (ms)	**≥2 mg/kg** (n:35)	**<2 mg/kg** (n:39)	**p**
	391±18	397±21	0.200

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 (month)	-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