Archives of Epilepsy

Original Article

The Effect of Long-term Levetiracetam Use on Changes in ECG in Patients with Pediatric Epilepsy

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Cite this article as: Aydın H, Korkut O. The effect of long-term levetiracetam use on changes in ECG in patients with pediatric epilepsy. *Arch Epilepsy.* 2025;31(4):149-154.

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Received: 27.03.2025 **Accepted:** 07.07.2025 **Epub:** 23.10.2025 **Publication Date:** 07.11.2025

DOI: 10.4274/ArchEpilepsy.2025.25186

Abstract

Objective: Cardiovascular side-effects and arrhythmias can also be observed during levetiracetam use. The effects of levetiracetam on cardiac conduction and electrophysiology, and the probable effect mechanism are still unclear. The purpose of this study was to compare PR interval, QTc, QT interval, and QRS duration parameters on electrocardiography (ECG) performed before and on the second year of treatment, in patients diagnosed with epilepsy and started on levetiracetam monotherapy.

Methods: The files of 20 patients diagnosed with epilepsy who were started on levetiracetam therapy were examined in this study. Clinical findings, electroencephalography, cranial magnetic resonance imaging and ECG data of the cases before and at the twenty-fourth month of treatment were recorded.

Results: Twenty patients aged between five and 17 years (12.65±3.50) took part in the study. Comparison of the ECGs performed before the patients started treatment and in the second year of treatment revealed a pre-treatment mean QT value of 0.327±0.018 and a post-treatment value of 0.349±0.023. The increase was statistically significant (p=0.009). Comparison of pre- and post-treatment ECG parameters in terms of sex revealed that the pre-treatment PR interval was longer in males (p=0.031) and the QTc interval was longer in females (p=0.020).

Conclusion: Studies involving more cases are needed to examine the effects of long-term use of levetiracetam on the ECG.

Keywords: Seizure, levetiracetam, PR interval, QTc, QT interval, QRS duration, longtime

INTRODUCTION

Epilepsy is one of the most common neurological diseases, with a worldwide prevalence of approximately 1%.[1] The objectives of treatment are to suppress seizures, reduce their frequency, and improve the patient's quality of life.[2] Antiseizure drugs (ASDs) are employed for that purpose.[3]

Various mechanisms are implicated in the pathogenesis of the disease, including ion channel dysfunction. Ion channels represent the basis of neurons electrophysiological excitability and communication, while functional disturbance is thought to be capable of triggering epileptic seizures by affecting the excitability of the brain.[4]

Heart rate and blood pressure abnormalities may sometimes be seen in addition to seizures in patients with epilepsy.[5,6] While studies have suggested that epilepsy alters the QT interval and corrected QT interval (QTc), levetiracetam has been reported to exhibit a protective effect in the pediatric population.[7-10]

Levetiracetam is a safe and relatively low-cost drug capable of being used in various types of epilepsy, and one that exhibits less interaction with other antiseizure agents.[11] Its principal side-effects are nasopharyngitis, somnolence, headache, dizziness, fatigue, asthenia, diarrhea, and constipation, although severe side-effects, including Stevens-Johnson syndrome, liver failure, hepatitis, pancreatitis, hematological disorders, aggression, and attempted suicide can also be seen.[12-15] Cardiovascular side-effects and arrhythmias can also occur during levetiracetam use.[10] In recent years, it has been reported that it is capable of altering the QT interval and even causing torsades de pointes. CredibleMeds added levetiracetam to the list of drugs involving a risk of potential QT prolongation and torsades de pointes on 11 September 2022.[16-19]

The effects of levetiracetam on cardiac conduction and electrophysiology and the probable effect mechanism are still unclear. The purpose of this study was to compare heart rate (beats/min), PR interval, QTc, QT interval, and QRS duration parameters at electrocardiography (ECG) performed before treatment and in the second year of treatment on patients diagnosed with epilepsy and started on levetiracetam monotherapy.

METHODS

Study Design

The records of 20 individuals diagnosed with epilepsy on the basis of International League Against Epilepsy criteria at the Balıkesir University Medical Faculty Pediatric Neurology Clinic, Türkiye, between August 1, 2019, and December 1, 2022, and started on levetiracetam therapy were investigated retrospectively. Patients with additional chronic diseases (including hypertension, diabetes mellitus, congenital or acquired heart disease, and chronic lung disease), with histories of the use of different drugs (such as macrolides, antipsychotics, antidepressants, antihistamines, or anti-arrhythmic drugs), who were not using levetiracetam regularly, or who were using polytherapy, were excluded.

Clinical findings and electroencephalography (EEG), cranial magnetic resonance imaging (MRI), and ECG data before and after two years of treatment were recorded for all cases.

Standard 12-lead ECGs were performed for all patients in the supine position, using a machine set at a paper speed of 25 mm/s and a calibration of 10 mm/mV. The recordings were obtained at rest and in a quiet environment. The duration of each ECG session was approximately 1-2 minutes. ECGs were manually interpreted by the same clinician to minimize interobserver variability. The following parameters were measured: heart rate, PR interval, QRS duration, QT interval, and QTc; with QTc values calculated using the Bazett formula. ECG parameters were evaluated according to gender and age groups. In the literature, age 12 has been identified as a critical threshold at which QTc interval alterations become more prominent in both male and female children. Based on these findings, age 12 was adopted in our study as a cut-off point to assess age-related effects on QTc changes.[20] Before starting the study, the necessary approval was obtained from the Clinical Research Ethics Committee of Balıkesir University Faculty of Medicine (approval no: 2022/145, date: 07.12.2022).

Statistical Analysis

Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA). Descriptive parameters were analyzed in all patients and by sex. After testing for normality of data distribution, ECG parameters heart rate (beats/min), PR, QTc, QT, and QRS were measured in all patients and were compared before and after treatment using the Wilcoxon and Mann-Whitney U tests.

RESULTS

Twenty patients aged between five and 17 years (mean age 12.65±3.50) took part in the study. The majority were girls, which constituted 11 individuals (55%). The great majority of patients had generalized type seizures (16, 80%), the majority showed EEG findings (15, 75%), and most had normal cranial MRI (16, 80%). Among the 20 patients, EEG findings were abnormal in 15 cases. Of these, 8 patients exhibited focal epileptiform discharges, while 7 had generalized epileptiform discharges. Cranial MRI was abnormal in 3 patients (e.g., arachnoid cyst, periventricular leukomalacia, cortical malformation) (Table 1).

Comparison of the ECGs performed before the patients started treatment and after 24 months revealed a pre-treatment mean QT value of 0.327±0.018 and a post-treatment QT value of 0.349±0.023. The pre-treatment heart rate was 97.8±11.77 (78-120) beats/min, and the post-treatment heart rate was 82.25±16.78 (59-125) beats/min. These differences were statistically significant (p=0.009 and p=0.003, respectively). Pre-treatment PR interval, QTc, and QRS values were 0.139±0.021, 0.404±0.019, and 0.080±0.000, respectively, compared to 0.130±0.022, 0.400±0.023, and 0.075±0.016 after treatment. The differences between these values were not statistically significant (Table 2).

Comparison of pre- and post-treatment ECG parameters in terms of sex revealed a longer pre-treatment PR interval in boys and a longer QTc in girls (p=0.031 and p=0.020, respectively). There was no significant sex difference in pre- and post-treatment QT or QRS values (Table 3).

In terms of age, differences in pre- and post-treatment ECG parameters of heart rate and QT interval were statistically significant in the under-12 group (p=0.012 and p=0.04, respectively) (Table 4). In the over-12 age group, the ECG parameters of PR and QRS did not differ significantly before and after treatment (p=0.038 and p=0.034, respectively) (Table 5).

No cardiac side effect was observed in any patient.

Table 1. Demographic and laboratory characteristics of patients using levetiracetam

Age (years)	12.65±3.50
Sex	n, %
Male	9 (45%)
Female	11 (55%)
Age group	8 (40)
<12 years	12 (60)
>12 years	
Seizure type	n, %
Focal	4 (20%)
Generalized	16 (80%)
Electroencephalogram	n, %
Normal	5 (25%)
Abnormal	15 (75%)
- Focal epileptiform discharges	8 (40%)
- Generalized epileptiform discharges	7 (35%)
Cranial magnetic resonance imaging	n, %
Normal	16 (80%)
Abnormal	3 (15%)
- Arachnoid cyst,	1 (5%)
- Periventricular leukomalacia,	1 (5%)
- Cortical malformation	1 (5%)

MAIN POINTS

- Heart rate and blood pressure abnormalities may sometimes be seen in addition to seizures in patients with epilepsy
- While studies have suggested that epilepsy alters the QT interval and QTc, levetiracetam has been reported to exhibit a protective effect in the pediatric population.
- Cardiovascular side-effects and arrhythmias can also occur during levetiracetam use. The effects of levetiracetam on cardiac conduction and electrophysiology and the probable effect mechanism are still unclear.

Table 2. A comparison of ECG parameters before and after levetiracetam therapy

	Pre-treatment mean±SD (min-max)	24 months post-treatment mean±SD (min-max)	p-value
Heart rate (beats/min)	97.8±11.77 (78-120)	82.25±16.78 (59-125)	0.003
PR interval (s)	0.139±0.021 (0.12-0.18)	0.130±0.022 (0.10-0.20)	0.084
QTc (s)	0.404±0.019 (0.36-0.45)	0.400±0.023 (0.35-0.43)	0.447
QT (s)	0.327±0.018 (0.32-0.38)	0.349±0.023 (0.28-0.40)	0.009
QRS (s)	0.080±0.000 (0.08)	0.075±0.016 (0.06-0.10)	0.166

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

Table 3. A comparison of ECG parameters before and after levetiracetam therapy between the sexes

	Pre-treatment mean±SD (min-max)			24 months post-treatment mean±SD (min-max)		
	Female	**Male**	**p-value (pre)**	**Female**	**Male**	**p-value (post)**
Heart rate (beats/min)	98.09±12.82 (80-120)	97.44±11.11 (78-110)	0.882	91.09±14.24 (77-125)	71.44±13.27 (59-97)	0.06
PR interval (s)	0.129±0.016 (0.12-0.16)	0.151±0.020 (0.12-0.18)	0.031	0.129±0.026 (0.10-0.20)	0.131±0.018 (0.12-0.16)	0.656
QTc (s)	0.410±0.018 (0.39-0.45)	0.396±0.019 (0.36-0.42)	0.201	0.410±0.017 (0.37-0.43)	0.387±0.024 (0.35-0.43)	0.020
QT (s)	0.329±0.021 (0.32-0.38)	0.324±0.013 (0.32-0.36)	0.766	0.340±0.030 (0.28 -0.36)	0.360±0.035 (0.28-0.40)	0.175
QRS (s)	0.080±0.000 (0.08)	0.080±0.000 (0.08)	0.1	0.080±0.015 (0.06-0.10)	0.069±0.015 (0.06-0.10)	0.131

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

Table 4. A comparison of ECG parameters before and 24 months after treatment in patients under 12 using levetiracetam

	Pre-treatment mean±SD (min-max)	Post-treatment, 24 months mean±SD (min-max)	
	<12 years	**<12 years**	**p-value**
Heart rate (beats/min)	98.25±8.32 (86-110)	79±13.76 (59-100)	0.012
PR interval (s)	0.145±0.0233 (0.12-0.18)	0.14±0.028 (0.10-0.20)	0.581
QTc (s)	0.408±0.024 (0.39-0.43)	0.405±0.02 (0.37-0.43)	0.546
QT (s)	0.327±0.021 (0.32-0.38)	0.355±0.025 (0.32-0.40)	0.040
QRS (s)	0.080±0.000 (0.08)	0.083±0.016 (0.1)	0.655

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

Table 5. A comparison of ECG parameters before and 24 months after treatment in patients over 12 using levetiracetam

	Pre-treatment mean±SD (min-max)	Post-treatment, 24 months mean±SD (min-max)	
	>12 years	**>12 years**	**p-value**
Heart rate (beats/min)	97.5±13.97 (78-120)	84.42±18.78 (59-125)	0.05
PR interval (s)	0.135±0.019 (0.12-0.16)	0.123±0.014 (0.10-0.20)	0.038
QTc (s)	0.40±0.022 (0.36-0.45)	0.395±0.025 (0.35-0.43)	0.590
QT (s)	0.326±0.015 (0.32-0.36)	0.345±0.037 (0.28-0.40)	0.094
QRS (s)	0.080±0.000 (0.08)	0.083±0.016 (0.1)	0.034

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

DISCUSSION

The electrical stimulation of various regions of the brain may cause cardiac rate and rhythm abnormalities. The most common types of cardiac autonomic dysfunction associated with seizures are tachyarrhythmia, bradyarrhythmia, and ECG changes.[21] Some studies have shown an association between seizure disorders and QTc prolongation, but have reported no change in mean QTc interval regardless of the duration of the disease, its frequency, or type.[5,7,22] The mechanism involved in QTc interval prolongation is not yet fully understood.[23,24] In addition to seizures and autonomic dysfunction, studies have reported that changes in cardiac electrophysiology may also derive from pathophysiological factors, including the ion channels underlying the disease.[25,26] Similar underlying pathophysiological electrical mechanisms are present in cardiac arrhythmias and epilepsy. Electrical activity disturbance in different tissues plays a role in the pathogenesis of both diseases.[27] Ion channels are also known to be involved in their pathogenesis. In addition, in epileptic children diagnosed with idiopathic or cryptogenic seizure disorder, there is evidence of genetic mutations in ion channels.[28] Darbin et al.[29] found that the severity of convulsive seizures and seizure recurrence constitute determinants of disordered cardiac autonomic regulation and directly affect the duration of cardiac arrhythmia during the immediate postictal state.

The effect of ASDs on the heart can be unpredictable. While they can prevent sudden unexpected death in epilepsy (SUDEP) by improving seizure control, they can also potentially contribute to SUDEP if they are suddenly withdrawn or by exerting direct effects on cardiac control.[30] Although the mechanism involved in the cardiovascular effects emerging in association with levetiracetam use has not yet been fully established, the current focus is on potential mechanisms. The first of these involves the effect of the drug on autonomic nervous system functions. Barrueto et al.[31] reported that a number of findings associated with levetiracetam use involved autonomous functions. Page et al.[32] also attributed bradycardia and hypotension developing in association with levetiracetam use to increased muscarinic activity in the autonomic nervous system. The stimulation of M2 muscarinic receptors leads to bradycardia, and the activation of M3 muscarinic receptors can result in vasodilatation and hypotension.[32] The confirmation by Oliveira et al.[33] that levetiracetam exhibits agonist activity against M2 receptors supports this probable mechanism. Lukkarinen et al.[34] also reported improvement with levetiracetam in a patient with recurrent sinus arrest and asystole due to breath-holding spells and concluded that it may be of therapeutic importance in regulating disease-related autonomic system dysfunction. However, Yılmaz and Çiğdem[35] reported that levetiracetam had no significant effect on autonomic nervous system functions, either in monotherapy or in polytherapy. Another mechanism capable of causing changes in cardiac conduction is drug-related inhibition of the potassium ion channel flow. Levetiracetam is reported to inhibit the flow of potassium ions, which may lead to prolongation of the QT interval, as well as cardiac arrhythmia and sudden death.[36] PR and QTc prolongation observed by Krishnan and Krishnamurthy[17] in male patients receiving polytherapy and linked to levetiracetam, the pre-treatment PR (0.139±0.021) and QTc (0.404±0.019) values in the present study decreased after treatment (to 0.130±0.022 and 0.400±0.023, respectively), although the differences were not statistically significant. In addition, this decrease was present in all patients, including men.[17] In the study by Altun and Yasar,[24] the heart apex beat, QT, and QTc parameters of patients with epilepsy using levetiracetam differed significantly from the pre-treatment values. However, Hulhoven et al.[37] described the effect of levetiracetam on the QT interval as negligible. Siniscalchi et al.[38] also reported that levetiracetam had no effect on the PR interval in healthy individuals, but exhibited negative effects on QT/QTc. Phenobarbital has been shown to prolong the QTc interval more than levetiracetam in patients.[38] In the present study, a decrease in heart rate and prolongation of the QT interval were observed in the 24th month post-treatment compared to pre-treatment values. In terms of gender, the pre-treatment PR interval was longer in boys, while the post-treatment QTc was shorter. In the under-12 age group, a decrease in heart rate and prolongation of the QT interval were determined post-treatment, while in the over-12 age group, a decrease in heart rate, shortening of the PR interval, and prolongation of QRS were observed.

While some cases have exhibited no noteworthy side effects as a result of high-dose levetiracetam use, others have resulted in vomiting, loss of consciousness, decreased deep tendon reflexes and hypotonia, somnolence, altered consciousness, respiratory depression, and coma.[39,40] Since levetiracetam does not block sodium channels, it is regarded as a relatively safer ASD in terms of cardiotoxicity.[41] Indeed, studies have reported that overdoses cause no cardiovascular toxicity in children or adults, and no changes in ECG or blood pressure in healthy individuals.[40,42,43] Gurgul et al.[44] reported that levetiracetam exhibits protective features against neonatal hypoxic-ischemic injury-induced deteriorations in adulthood, in terms of ventricular contractility and ultrastructural and mitochondrial damage in the myocardium. In the most recent study on the subject, Cross et al.[10] compared cases using levetiracetam and oxcarbazepine in terms of cardiac effects (SUDEP and arrhythmia) and reported no relationship between levetiracetam and sudden cardiac death or ventricular arrhythmia.[44] However, some studies have shown that overdose with levetiracetam may affect cardiac electrophysiology and rhythm.[45] Page et al.[32] reported the development of cardiotoxicity in the form of bradycardia and hypotension, in a woman who was taking 60-80 g levetiracetam. Another study reported bidirectional ventricular extrasystoles with sinus bradycardia in a patient receiving high-dose levetiracetam for attempted suicide, and noted that the patient was normotensive at follow-ups.[45] No cardiac side effect associated with the use of levetiracetam at a normal dose range was observed in any of the patients in this study.

Study Limitations

ECG findings change rapidly from birth through childhood, with age differences clearly related to increasing QRS voltages and a widening QRS complex. The only sex difference at this age is a slightly longer QRS duration in boys than in girls. In adulthood, sex differences in QRS voltage are greatest in the under-40 age group and tend to decrease with advancing age. QRS duration is longer in males than in females, but this difference is rarely utilized in terms of diagnostic criteria. The QTc interval is longer in females than in males.[46] Numerous factors which may prolong the QT interval should be checked whenever QTc prolongation is observed. These include drugs, electrolyte imbalances, hormonal influence, and comorbidities.[47] Due to the low sample size in the present study, ECG parameters could not be evaluated across different age groups

by gender. In addition to its retrospective, single-center design, this study has several limitations. These include the relatively recent establishment of the pediatric neurology department at our hospital, the short study duration of two years, and the limited sample size, partly due to irregular follow-up by some patients. Furthermore, ECG evaluations were not conducted blinded, and the ECG parameters could not be assessed by a pediatric cardiologist due to the unavailability of one at our institution during the study period. Lastly, the absence of a control group further limits the generalizability of the findings.

CONCLUSION

Levetiracetam is frequently prescribed by physicians due to its antiepileptic activity against various types of seizure, its efficacy, easy accessibility, and safety profile. The data from this study show that although the use of levetiracetam at therapeutic doses causes changes in ECG parameters depending on age group and sex, no levetiracetam-related cardiac side-effects were observed in any patients. Further prospective clinical studies involving more centers and cases are now needed in this area.

Ethics

Ethics Committee Approval: Before starting the study, the necessary approval was obtained from the Clinical Research Ethics Committee of Balıkesir University Faculty of Medicine (approval no: 2022/145, date: 07.12.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: H.A., O.K., Design: H.A., O.K., Data Collection or Processing: H.A., Analysis or Interpretation: O.K., Literature Search: H.A., O.K., Writing: H.A., O.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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