Archives of Epilepsy

Original Article

Electrocardiographic Evaluation in Patients Receiving Lamotrigine Monotherapy/Duotherapy

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Cite this article as: Ser MH, Türk BG, Ser ÖS, Yeni SN. Electrocardiographic Evaluation in Patients Receiving Lamotrigine Monotherapy/Duotherap. *Arch Epilepsy.* 2023;29(4):105-110.

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Received: 10.02.2023 **Accepted:** 07.03.2023 **Publication Date:** 22.11.2023

DOI: 10.4274/ArchEpilepsy.2023.23079

Presented in: The abstract of the manuscript was presented in the 13th National Epilepsy Congress, Turkey in 2022.

Abstract

Objective: Despite its widespread use and safety data, the cardiac safety of lamotrigine was brought into question in October 2020 when the U.S. Food and Drug Administration issued a safety warning about its cardiac side effects. Here, we investigated whether there are differences in electrocardiogram (ECG) findings between epilepsy cases receiving lamotrigine monotherapy and those receiving duotherapy.

Methods: Patients older than 16 years who were followed up with a diagnosis of epilepsy and receiving lamotrigine were retrospectively identified. Those receiving only lamotrigine and any second anti-seizure medication (ASM) in addition to lamotrigine were included in the study, and those receiving more than two ASMs were excluded. Eligible patients were asked to apply to any health institution and have an ECG performed. Heart rate, PR distance, QRS duration, QT duration, corrected QT value, and Tp-Tend value were calculated manually, and ST-T changes were evaluated. Comparisons were made between patients receiving monotherapy and dootherapy and those receiving low-dose and high-dose lamotrigine.

Results: There were 19 patients receiving monotherapy and 11 receiving duotherapy. The ECG parameters of all other patients were within normal values. When ECG parameters were compared between patients receiving monotherapy and those receiving duotherapy, no significant differences were found in heart rate, PR distance, QRS duration, QT duration, QTc duration, Tp-Tend duration, and presence of ST-T changes. When the patients were divided into low-dose and high-dose lamotrigine groups, there were no significant differences in the ECG parameters between these two groups.

Conclusion: The relationship between the use of lamotrigine and cardiac conduction problems in patients with epilepsy has attracted the attention of physicians since its introduction into clinical practice. Although our results did not indicate a significant relationship, there is still a need to determine the risk groups and clarify the pathophysiology of lamotrigine-related arrhythmia through genotype- and phenotype-related studies.

Keywords: Cardiac conduction disorders, cardiac side effect, electrocardiography, lamotrigine, neurology

INTRODUCTION

Lamotrigine has been widely used as an anti-seizure medication (ASM) since 1994.[1] It acts by modulating voltage-gated sodium channels. Accordingly, lamotrigine prevents the pathologically continuous, high-frequency, repetitive firing of voltage-gated sodium channels and reduces presynaptic glutamate release. This effect inhibits the glutamate-mediated action potential. Thus, it suppresses neuronal hyperexcitability and prevents seizure occurrence.[2,3]

Despite its widespread use and safety data, the cardiac safety of lamotrigine was brought into question in October 2020 when the U.S. Food and Drug Administration (FDA) issued a safety warning about the cardiac side effects of lamotrigine. This warning was rooted in the fact that lamotrigine exhibits class IB antiarrhythmic activity at therapeutically relevant concentrations through the inhibition of human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependance Although it did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study, it could slow ventricular conduction (widen QRS) and induce proarrhythmia, including sudden death, in patients with structural heart disease or myocardial ischemia.[4,5] Therefore, this warning addressed the cardiac risk group, stating that therapeutic levels of lamotrigine in individuals with any structural or functional heart disease might cause life-threatening arrhythmias. The term “structural or functional heart diseases” indicates heart valve diseases, heart failures, a history of cardiac ischemia, cardiac conduction disorders (second- and third-degree heart block), ventricular arrhythmias, congenital heart diseases, Brugada syndrome, and similar channelopathies, along with any coronary artery disease risk factors without a history of cardiac disease.

It has also been reported that the simultaneous use of a different sodium channel blocker increases this effect.[6] It was emphasized that this effect is not observed in healthy individuals but may occur in those with any of the above-mentioned cardiac disorders, which can be considered a risk factor for arrhythmia.[4]

Thereafter, the International League Against Epilepsy and American Epilepsy Association established the Task Force on the Cardiac Effects of Lamotrigine and released an advisory for healthcare professionals regarding the use of lamotrigine and monitoring cardiac side effects. The study group listed their recommendations under two headings. First, the presence of asymptomatic heart disease would be very rare in individuals under 60 years of age, and in the absence of cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, and smoking, the risk would be negligible. Therefore, electrocardiography (ECG) before lamotrigine treatment is recommended only in patients younger than 60 yearsof age. Because the risk of asymptomatic cardiac conduction disorders increases in patients over 60 years of age, ECG is recommended before starting lamotrigine in all patients in this group and should be repeated after increasing to the target dose if necessary. In addition, for patients currently receiving lamotrigine therapy, ECG and cardiology consultation should be performed in cases of sudden syncope or presyncope with loss of muscle tone if there is no clear vasovagal/orthostatic cause.[7]

A standard 12-lead ECG provides prognostic information about current and future cardiac events through parameters such as heart rate, PR distance, QT duration, corrected QT value (QTc), Tp-Tend value, and ST-T changes. In many studies, it has been observed that a short PR distance increases all-cause mortality and undesirable cardiovascular events.[8] A prolonged QRS duration usually indicates the presence of changes in the myocardium due to underlying heart disease and is generally associated with decreased ejection fraction or enlarged left ventricular volumes.[9] Heart rate-QTc is the classical method for assessing cardiac repolarization time. A prolonged QTc interval is associated with a higher risk of death in patients with coronary heart disease and in the general population.[10] The Tp-Tend value is the interval from the peak of the T wave at the end of the T wave and is considered a distribution index of ventricular repolarization. Prolonged Tp-Tend interval has been associated with arrhythmia, sudden cardiac death, and increased cardiovascular mortality.[11]

Considering the current but unclear report of cardiac adverse events of lamotrigine, we aimed to investigate whether there are significant changes in the ECG findings of epilepsy cases receiving lamotrigine monotherapy versus myotherapy and low-dose versus high-dose lamotrigine therapy.

MAIN POINTS

- Lamotrigine use may result in Brugada-like cardiac conduction problems.
- Increased neuronal sodium channel expression in cardiac tissue was revealed to cause Brugada-like conduction disorders by increasing the affinity of lamotrigine for cardiac sodium channels in epileptic mice.
- Post-lamotrigine upregulation of pathogenic sodium channel proteins in cardiac tissue may explain this side effect in humans.
- There is a need to determine the risk groups and clarify the pathophysiological mechanism through genotype- and phenotype-related studies.

METHODS

Epilepsy cases followed up in a tertiary healthcare center were included in the study. The İstanbul Training and Research Hospital Local Ethical Committee approved the study (decision no: 266, date: 13.10.2023), and a written patient consent form was obtained. Patients older than 16 years who were receiving lamotrigine treatment were retrospectively identified by examining their medical records. Among them, patients receiving lamotrigine monotherapy or lamotrigine myotherapy with any second ASM were included in the study, whereas patients receiving more than two ASMs were excluded.

There were 400 patients receiving lamotrigine therapy; among them, 100 patients met the inclusion criteria. These patients were contacted by phone and informed about the study. Patients who gave consent were asked to apply to any health institution and have a 12-lead ECG performed and delivered to our center. Thirty had an ECG and were included in the study among these 100 patients. The ECG (paper speed 25 mm/sec and amplitude 10 mm/mV) results of all participants were examined by the same cardiologist. Heart rate, PR distance, QRS duration, QT duration, QTc value, and Tp-Tend value were calculated manually, and ST-T changes were evaluated. The Tp-Tend value was determined as the distance from the peak of the T wave at the end of the T wave. The calculated QT duration was corrected using the Bazett formula. In addition, branch blocks, atrioventricular conduction disorders, ST changes greater than 1 mm, T wave changes, and Brugada patterns on ECGs were investigated.[12,13]

Thirty patients were included in the study, and the following data were collected:

i. Demographics, medical history, and family history of sudden cardiac death.

ii. Seizure onset age, seizure type, epilepsy etiology, daily dose of lamotrigine, duration of lamotrigine use, and additional drugs.

iii. Heart rate, PR interval, QRS width, QT distance, QTc, Tp-Tend distance, and ST change on ECG.

Statistical Analysis

Data analyses were performed using the GraphPad Prism 8.4.3 software statistical package. The data distribution was not normal. We compared demographic and clinical data between patients receiving monotherapy and dootherapy and low-dose and high-dose lamotrigine. We used the chi-square test for qualitative data. A p value ≤ 0.05 was considered significant.

RESULTS

A total of 30 patients participated in the study. The demographic and clinical data of the study groups are presented in Table 1. The mean age of the patients was 31.6±8.5 years [minimum-maximum (min-max): 16-48 years]. With the exception of one patient who had hypothyroidism, none of the patients had any known chronic disease or smoking history that could be a cardiovascular risk factor.

The daily lamotrigine dose for the entire patient group was 200±116.8 mg. There were 19 patients receiving monotherapy,

and the daily dose of lamotrigine for this group was 207.9±106.7 mg. The number of patients receiving myotherapy was 11, and the daily dose of lamotrigine was 228±152 mg for this group. The ASMs used in myotherapy were valproic acid, carbamazepine, levetiracetam, and pregabalin. The duration of lamotrigine use for the entire patient group was 6.8±4.6 years (min-max: 2-18 years). This period was 6.16±3.7 years (min-max: 2-12 years) for patients receiving monotherapy and 7.9±5.7 years (min-max: 2-18 years) for patients receiving dootherapy. There was no significant difference between the two groups regarding the mean lamotrigine dose and duration of use.

When the ECG parameters were evaluated, one patient, whose daily lamotrigine dose was 300 mg/day, had prolonged QT, QTc, and Tp-Tend durations. This patient was consulted by a cardiologist. Her repeated ECG was normal; therefore, the changes in the first ECG were attributed to reversible causes, such as electrolyte imbalance, rather than lamotrigine itself. The ECG parameters of all other patients were within normal values. When ECG parameters were compared between patients receiving monotherapy and duotherapy, no significant differences were found in the heart rate, PR distance, QRS duration, QT duration, QTc duration, Tp-Tend duration, and presence of ST-T changes (Table 2). Finally, the patients were divided into low-dose and high-dose lamotrigine groups; nevertheless, there were no significant differences in the ECG parameters between these two groups (Figure 1).

DISCUSSION

In this study, ECG parameters were used to evaluate the cardiac side effects of lamotrigine, revealing that there was no significant conduction disturbance associated with lamotrigine.

Although the FDA warning regarding the safety of cardiac side effects of lamotrigine is relatively recent, the information that sodium channel blockers can cause cardiac arrhythmia has long been known since studies had investigated lamotrigine-related cardiac conduction disorders before the FDA's warning. In 1994, the year lamotrigine was launched, Steinhoff et al.[14] followed up patients receiving lamotrigine with ECG recordings before and under medication. Interestingly, this study was designed following the observation of a patient with typical chest pain and repolarization disorder on ECG under lamotrigine treatment. However, they did not find a relationship between increased risk of cardiac side effects and lamotrigineuse.

Table 1. Demographic and clinical data of the patient population

Characteristic	Mean±SD
Age, year	31.6±8.5
Seizure onset, year	15.3±7.1
Sex, F (n, %)	25 (86%)
Epilepsy type	
- Generalized	17
- Focal	13
Antiseizure medication	
- Lamotrigine monotherapy	19
- Duotherapy	11
Family history of sudden cardiac death	0/30

SD: Standard deviation, F: Female

Table 2. Comparison of ECG characteristics of patients receiving lamotrigine monotherapy and duotherapy

Parameter	Monotherapy (n=19)	Duotherapy (n=11)	p value
	Mean±SD	Mean±SD	
Heart rate, beat/min	85.2±12.7	77.7±10.3	0.11
PR interval, ms	146.2±21.2	139.9±23.3	0.46
QRS duration, ms	83.6±9.8	83.5±10.9	0.99
QT duration, ms	351.2±28.6	364.8±24.7	0.20
QTc duration, ms	412.8±30.3	415.5±31.4	0.82
Tp-Tend duration, ms	80.7±12.4	82.9±14.9	0.67
ST-T change	0	0	

SD: Standard deviation, ECG: Electrocardiogram

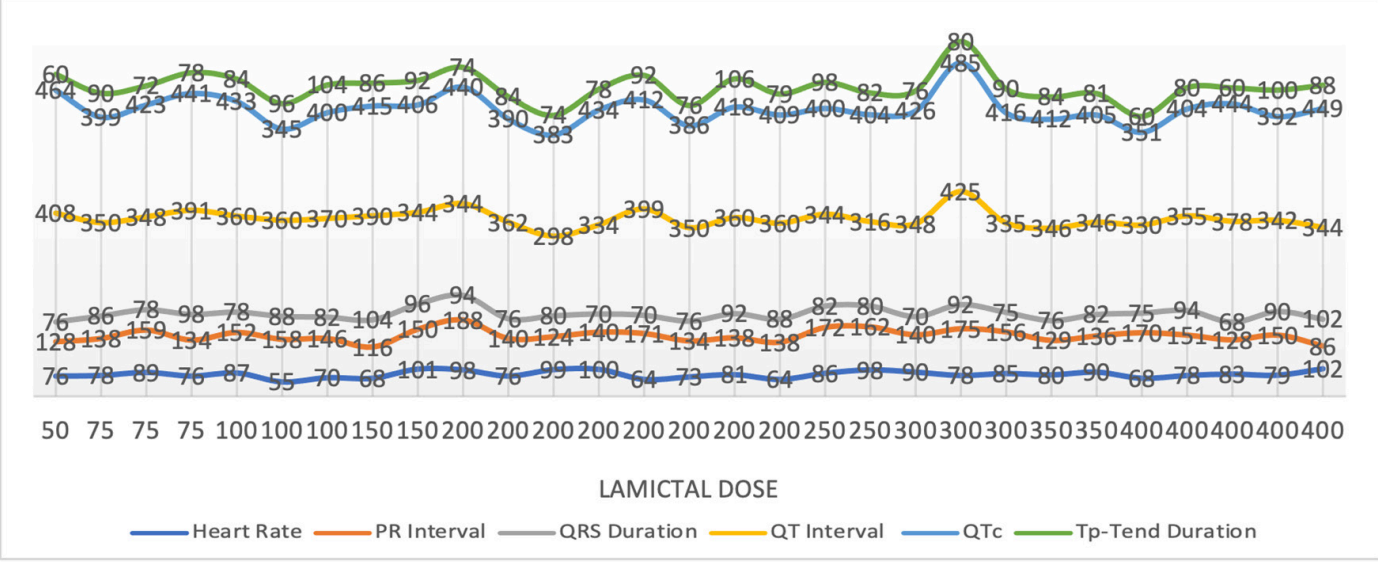

Figure 1. Electrocardiographic parameters of the study group according to lamotrigine dose

In a study on the effects of lamotrigine on ECG in healthy individuals, the drug was initiated with a daily dose of 100 mg and increased to 400 mg, and an average prolongation of the PR distance of 5 ms (normal range: 120-200 ms) was observed, which was negligible.[15] The researchers concluded that the maximum effect of lamotrigine on PR was reached at certain doses and did not increase in a dose-dependent manner because the prolongation of the PR distance was similar at medium and high doses. Furthermore, when QT and QTc durations were examined in the same population, lamotrigine at therapeutic doses did not cause prolonged QT and QTc.[5] Both studies were conducted in healthy young people. In another study conducted in patients over 65 years of age, ECG was performed before and at the 40th week of treatment. Heart rate, QTc, and QRS duration were examined, and no significant ECG changes were observed.[16]

Another concern raised by lamotrigine-related cardiac side effects is that it may be associated with sudden unexpected death in epilepsy (SUDEP). Although the exact cause of SUDEP is unknown, it has been associated with cardiac arrest resulting from respiratory failure in the peri-ictal period.[17] Concomitant cardiac arrhythmia is a risk factor for SUDEP.[18] These findings raise the question of whether the adverse side effects of lamotrigine on cardiac conduction are related to SUDEP. However, there are no definitive findings in the literature showing that any specific antiepileptic drug poses a greater risk for SUDEP than others. Current literature data indicate that SUDEP rates in lamotrigine use are similar to those in other studies.[19]

Although follow-up studies of the cardiac side effects of lamotrigine at therapeutic doses have not been associated with ECG changes indicative of cardiac conduction disturbance or SUDEP, case reports of lamotrigine overdose-related cardiac conduction disturbances and cardiac arrest cannot be disregarded, prompting researchers to further investigate this issue. In the first case report, changes suggestive of Brugada syndrome were detected on ECG of a female patient whose serum lamotrigine level was within a toxic range.[20] Diagnostic ECG changes for Brugada syndrome were observed after the procainamide challenge test. Following lamotrigine withdrawal, ECG was normal after repeated procainamide tests. The authors concluded that toxic doses of lamotrigine may affect cardiac sodium channels, causing drug-related Brugada syndrome.

In a case series, two of nine cases with lamotrigine overdose had prolongation of QRS and QTc on ECG, which was explained by cardiac sodium channel blockage associated with lamotrigine overdose.[21] Although sodium channel blockers, such as phenytoin and carbamazepine, might cause Brugada-type ECG changes, especially in those receiving polytherapy, the reports of patients receiving lamotrigine monotherapy are significantly higher than those of patients receiving other sodium channel blocker ASMs.[22-26] In addition, two of these reports observed ECG changes similar to those in patients with type 1 Brugada syndrome receiving therapeutic doses of lamotrigine.[27,28]

Since the warning in 2020, there have been numerous efforts to examine these side effects in population-based cohorts and systematic reviews. However, sufficient evidence could not be established yet.[29-32] Considering these findings, there is no significant evidence of an increased risk of cardiac arrhythmia with lamotrigine, according to both the literature and our study results. However, the presence of cases receiving therapeutic lamotrigine levels and with Brugada syndrome-like ECG changes cannot be disregarded. At this point, two questions need to be answered:

1) Why does this effect come to the fore with lamotrigine rather than with other sodium channel blockers?

2) Who are the high-risk groups?

Evidence that may answer the first question has come from animal studies. In 2012, Biet et al.[33] studied sodium channel isoforms responsible for producing electrical impulses in the cardiac tissue of canine cardiac muscle. They showed that sodium channels in canine cardiac muscle tissue comprised not only the cardiac isoform NaV 1.5 but also noncardiac isoforms, including neuronal ones. The authors suggested that the overexpression of noncardiac isoforms may be associated with arrhythmias with a prolonged QT interval. Subsequently, in a study published in 2015, it was shown that neuronal sodium channel isoforms were upregulated in the heart tissue and brain in epileptic mice compared with the control group.[34] Finally, following the FDA's warning in 2020, increased neuronal sodium channel expression in the cardiac tissue of epileptic mice was revealed to cause Brugada-like conduction disorders by increasing the affinity of lamotrigine for cardiac sodium channels.[35] The authors showed a decrease in lamotrigine-related cardiac excitability in epileptic mice, whereas there was no significant change in healthy mice, despite receiving the same drug. Although it is unclear whether these findings are valid for humans, they may partially shed light on the issue in question.

Regarding the second question on at-risk individuals, Brugada syndrome needs to be examined, given that cardiac conduction disorders and Brugada syndrome cases come to the fore with lamotrigine. Brugada syndrome is a rare, inherited disease that increases the risk of sudden cardiac death and arrhythmias despite a structurally normal heart. Diagnosis is based on a distinctive ECG finding spontaneously or after the administration of a sodium channel blocker (challenge test).[36] This cardiac conduction disorder, first described in 1992, was first associated with the *SCN5A* gene encoding the cardiac sodium channel. Today, at least 18 loci are associated with the complex polygenic inheritance of the condition.[37] There are reports of family members with the same genetic mutation but without the phenotype,[38] which suggests that lamotrigine may cause ECG changes by revealing phenotypic features with an additive impact. Therefore, if the use of lamotrigine might be arrhythmogenic in individuals with mutations that are not reflected in the phenotype, it seems reasonable to check for any changes that indicate a conduction disorder by performing ECG before the treatment. If the mechanisms proven by animal experiments are also valid for humans, post-lamotrigine upregulation of pathogenic sodium channel proteins in cardiac tissue might be another explanation for this side effect. In addition, genetic examinations in patients who develop cardiac side effects upon lamotrigine treatment are likely to shed light on the current uncertainties and the common pathophysiological mechanism causing Brugada syndrome and epilepsy.

Study Limitations

The most significant limitation of our study is the inadequate number of patients. However, our results are not different from those in the above-mentioned more comprehensive studies conducted with a similar methodology.

CONCLUSION

The relationship between the use of lamotrigine in patients with epilepsy and Brugada-like cardiac conduction problems has attracted the attention of physicians since the drug was introduced into clinical practice; however, it has been under the microscope only since 2020, following FDA warning. There is still a need to determine the risk groups and clarify the pathophysiological mechanism through genotype- and phenotype-related studies.

Ethics

Ethics Committee Approval: The İstanbul Training and Research Hospital Local Ethical Committee approved the study (decision no: 266, date: 13.10.2023).

Informed Consent: Written patient consent form was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H.S., B.G.T., S.N.Y., Concept: S.N.Y., Design: S.N.Y., Data Collection or Processing: M.H.S., B.G.T., Ö.S.S., Analysis or Interpretation: Ö.S.S., Literature Search: M.H.S., B.G.T., Ö.S.S., Writing: M.H.S., S.N.Y.

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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