Effects of Lithium Therapy on Ventricular Repolarization in Bipolar Disorder Patients

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ABSTRACT

Introduction: Bipolar disorder (BD) is a significant mental health concern in the world. Most of the drugs used in the treatment of bipolar disease may cause life-threatening arrhythmias by affecting the distribution of ventricular repolarization (VR). VR is commonly assessed using QT interval and Twave measurements. The aim of this study was to evaluate VR using the T peak to T end (Tp-e) interval and the Tp-e/QT ratio and to investigate the relationship between lithium therapy and VR parameters in patients with BD.

Patients and Methods: Forty-six BD patients under lithium therapy and 45 participants in a control group were included in our study. The Tp-e interval and Tp-e/QT ratio were measured using 12derivation electrocardiography (ECG). These parameters were compared between groups.

Results: The QT interval (p= 0.01), QTc interval (p= 0.003), Tp-e interval (p< 0.001), and Tpe/QT ratio (p= 0.009) were significantly higher in patients with BD than in the control group. There was a positive correlation between the Tp-e interval and serum lithium levels (r= 0.317, p< 0.032). In addition, the increased serum lithium level (β= 0.398, p= 0.007) was found to be an independent predictor of the prolonged Tp-e interval.

Conclusion: Prolonged Tp-e interval may be a useful indicator of increased risk of ventricular arrhythmia in patients using lithium therapy.

Key Words: Bipolar disorder; lithium; Tp-e interval; ventricular repolarization

Bipolar Bozukluk Hastalarında Lityum Tedavisinin Ventriküler Repolarizasyon Üzerine Etkileri

ÖZET

Giriş: Bipolar bozukluk (BD) dünyada önemli bir mental sağlık sorununudur. Bipolar bozukluk tedavisinde kullanılan ilaçların çoğu, ventriküler repolarizasyonun (VR) dağılımını etkileyerek hayatı tehdit eden aritmilere neden olabilir. VR genellikle QT aralığı ve T dalgası ölçümleri kullanılarak değerlendirilir. Bu çalışmanın amacı, Tp-e intervali ve Tp-e/QT oranını kullanarak VR'yi değerlendirmek ve bipolar bozukluğu olan hastalarda lityum tedavisi ve VR parametreleri arasındaki ilişkiyi araştırmaktır.

Hastalar ve Yöntem: Çalışmamıza lityum tedavisi alan 46 hasta ve 45 katılımcıdan oluşan kontrol grubu dahil edildi. Tp-e aralığı ve Tp-e/QT oranı 12-derivasyon elektrokardiyografi (EKG) kullanılarak ölçüldü. Bu parametreler gruplar arasında karşılaştırıldı.

Bulgular: Bipolar bozukluk olan hastalarda QT interval (p= 0.01), QTc interval (p = 0.003), Tp-e interval (p< 0.001) ve Tp-e / QT oranı (p= 0.009) kontrol grubuna göre anlamlı olarak yüksek bulundu. Tp-e intervali ile serum lityum düzeyleri arasında pozitif korelasyon vardı (r= 0.317, p< 0.032). Ayrıca artmış serum lityum seviyesi (β= 0.398, p= 0.007), uzun Tp-e aralığının bağımsız bir belirleyicisi olarak bulundu.

Sonuç: Uzamış Tp-e intervali, lityum tedavisi kullanan hastalarda artmış ventriküler aritmi riskinin yararlı bir göstergesi olabilir.

Anahtar Kelimeler: Bipolar bozukluk; lityum; Tp-e interval; ventriküler repolarizasyon

INTRODUCTION

Bipolar disorder (BD) is a complex and chronic disease characterized by acute dysfunctional mood states, alternating between mania or hypomania and depression. Lithium is still recommended as a first line drug in the treatment of BD. However, its narrow therapeutic range increases the risk of intoxication and limits the widespread use of lithium in daily practice. Various electrocardiographic (ECG) changes, such as sinus bradycardia, sinoatrial

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block, complete heart block, premature ventricular contractions, and prolongation of ventricular repolarization (VR), have been associated with lithium overdose[1-4]. Prolongations of QT and T peak to T end (Tp-e) intervals and two VR parameters have been described as markers for the development of life-threatening ventricular arrhythmias and sudden death[5,6]. According to the current evidence, a possible mechanism of the action for lithium's cardiac side effects is the influence on the sodium-potassium pump, which is blocked by lithium[7].

Some drugs, such as antipsychotics (especially thioridazine, pimozide, and lithium), psychotropics, and antidepressants (especially tricyclic antidepressants), may cause an increase in the distribution of VR[8]. Recently, some VR markers, such as QT interval (QT), corrected QT (QTc), QT dispersion (QTd), Tp-e interval (Tp-e), and Tp-e/QT ratio, have been found to be useful in predicting life-threatening ventricular arrhythmias in clinical disorders without structural heart disease. Some studies have shown that increased Tp-e and Tp-e/QT were related to the elevated risk of malignant ventricular arrhythmias[9-11]. The effects of lithium on the QT interval have been investigated in several studies[12,13]. However, to the best of our knowledge, the data on the Tp-e interval and Tp-e/QT ratio in BD patients are insufficient. The aim of this study was to evaluate VR using the Tp-e interval and Tp-e/QT ratio and to investigate the relationship between lithium therapy and these electrocardiographic VR parameters in patients with BD.

PATIENTS and METHODS

Study Population

A total of 91 participants were enrolled in the study. Fortysix in patients with BD in the remission period provided informed consent to the attending psychiatrists. The control group was composed of 45 healthy participants. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria[14]. All patients had been in the remission period for at least 2 months. Healthy participants were selected among individuals who were admitted to the department of cardiology outpatient unit for a routine check-up. Physical examination, medical history of patients, and blood biochemistry were evaluated in both groups to exclude systemic diseases.

We designed this study to exclude BD patients and healthy participants with other conditions that prolong QT interval. Patients with hyperthyroidism, hypothyroidism, malignancy, chronic lung diseases, hepatic or renal dysfunction, heart failure, pulmonary hypertension, acute coronary syndrome, hypertrophic or dilated cardiomyopathies, congenital heart diseases, non-sinus rhythms, previous history of myocardial infarction, and electrolyte imbalance were excluded from the study. BD patients using other medications that could prolong QT were also excluded.

Blood samples were collected 12 hours after administration of the last dose of lithium treatment, and meantime ECG and echocardiography were performed. Serum lithium concentration (ng/dL), serum creatinine (mg/dL), and serum electrolytes were measured in blood samples.

The present study was cross-sectional and observational. It was carried out in a single center and was approved by the local ethics committee. All participants of the control group also provided written informed consent.

Electrocardiography

Twelve-derivation ECGs were obtained at rest, with 10 mm/mV amplitude and 25 mm/sec (Cardiofax V; Nihon Kohden Corp., Tokyo, Japan) rate with the patient in the supine position and breathing freely. All the ECGs were transferred to a computer system via a scanner, and ×400% magnification was carried out using the Adobe Photoshop software. All parameters were digitally measured by two cardiologists blinded to the status of each participant. A third blinded cardiologist verified all the results. The average value of three examinations was calculated for each derivation.

QT and R-R intervals were measured in all derivations. The QT interval was measured between the beginning of the QRS complex and the end of the T wave and was corrected (QTc) according to the heart rate using the Bazett formula, and derivation V2 was selected for QT and QTc measurements[15]. The QTd was defined as the difference between the maximum and minimum QT intervals of the 12 derivations.

The Tp-e interval was measured via the tail method. In this method, the Tp-e interval was defined as the time from the peak of the T wave to the point the wave reached the isoelectric line leads[6,11]. Measurements of the Tp-e interval were performed using precordial derivations of ECG. The Tp-e and Tp-e/QT ratio were calculated from the V2 derivation. To improve the reliability of Twave offset determination, derivations with low-amplitude T waves (< 0.1 mV) were excluded from the analysis. The intraobserver and interobserver correlation coefficients for the Tp-e interval were 0.97 and 0.94, respectively, and for the Tp-e/QT ratio were 0.96 and 0.92, respectively.

All echocardiographic examinations were performed in the subjects using a 2.5-3.5-MHz transducer (General Electric Vivid S5, Milwaukee, WI, USA) in the left decubitus position. The left ventricle ejection fraction (LVEF) was calculated according to the Simpson method, and patients with LVEF above 55% were considered to have a normal systolic function.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 15.0 statistical program (SPSS Inc., Chicago, Ill.). Categorical variables are expressed as n (%), and continuous variables are expressed as mean ± standard deviation. Continuous variables were tested for normal

distribution using the Kolmogorov-Smirnov test. Differences between independent groups were assessed using the Student's t-test for normally distributed continuous variables and Mann-Whitney's U-test for variables without normal distribution. Categorical variables were assessed using the chi-square test. Relationships between parameters were determined using the Pearson's coefficient of correlation. Multivariate linear regression analysis was used to identify independent predictors of prolonged Tp-e interval. A p value < 0.05 was considered significant. To assess the predictive role toward the lithium effects of different cutoff values of VR measurements, a receiver operating characteristic (ROC) curve with calculations of area under the curve was constructed, and sensitivity and specificity values were calculated.

RESULTS

The clinical characteristics and the laboratory and echocardiographic parameters of the BD group and the control group are presented in Table 1. Age, sex, body mass index, creatinine, serum electrolytes, and LVEF values were similar between groups. The average daily lithium use and serum lithium level in patients with BD were 913 ± 209 mg and 0.704 ± 0.196 ng/dL, respectively.

The electrocardiographic parameters of the groups are shown in Table 2. The heart rate and QTd were similar between the two groups. QT and QTc intervals were significantly higher in patients using lithium therapy than those in the control group (p= 0.01 and p= 0.003, respectively). The Tp-e interval and Tp-e/QT ratio in patients using lithium therapy were significantly higher compared to the control group (p< 0.001 and p= 0.009, respectively). There was a statistically significant positive correlation between the Tp-e interval and serum lithium levels (r= 0.399, p= 0.006; Table 3, Figure 1). In the multivariate linear regression analysis, the increased serum lithium level (β= 0.398, p= 0.007) was found to be an independent predictor of prolonged Tp-e interval (Table 4).

The cut off value for lithium effects was determined using ROC curves (Tp-e > 99 ms; sensitivity, 78.0%; specificity, 73.0%; area under the curve, 0.79; 95% confidence interval,

Table 1. Clinical characteristics, laboratory values, and echocardiographic findings of the groups

	BD group (n= 46)	Control group (n= 45)	p
Age, years	38.3 ± 10.9	40.4 ± 15.9	0.464
Female, n (%)	20 (43)	23 (51)	0.466
Body mass index, kg/m^2	27.43 ± 4.58	26.13 ± 4.14	0.160
Systolic blood pressure, mmHg	118.4 ± 12.1	120.2 ± 15.9	0.543
Creatinine, mg/dL	0.79 ± 0.14	0.77 ± 0.11	0.399
Serum lithium level, ng/dL	0.704 ± 0.196		
Daily lithium dose, mg	913 ± 209		
Potassium, mEq/L	4.32 ± 0.42	4.18 ± 0.32	0.111
Sodium, mEq/L	139 ± 2	138 ± 2	0.289

Data are presented as mean ± SD or n (%). SD: Standard deviation, BD: Bipolar disorder.

Table 2. Electrocardiographic parameters of the study population

	BD group (n= 46)	Control group (n= 45)	p
Heart rate, beats/min	78.3 ± 17.3	74.8 ± 12.0	0.264
QT, ms	396.39 ± 27.77	377.23 ± 40.57	0.010
QTc, ms	412.79 ± 26.27	392.91 ± 34.85	0.003
QT maximum, ms	379.70 ± 31.11	370.44 ± 29.98	0.152
QT minimum, ms	348.59 ± 30.31	344.42 ± 28.01	0.489
QTd, ms	31.15 ± 14.00	25.93 ± 14.93	0.089
Tp-e interval, ms	105.78 ± 11.47	92.36 ± 12.71	< 0.001
Tp-e/QT	0.268 ± 0.033	0.247 ± 0.040	0.009

Data are presented as mean ± SD or n (%). MS: Milliseconds, QTc: Corrected QT, QTd: QT dispersion, Tp-e: T peak to T end interval, SD: Standard deviation, BD: bipolar disorder.

Table 3. The association between serum lithium levels and ECG parameters in bipolar disorder

	r	p
QT	0.159	0.468
QTc	0.468	0.110
QT maximum	0.145	0.335
QT minimum	0.085	0.574
QTd	0.006	0.968
Tp-e interval	0.399	0.006
Tp-e/QT	0.147	0.330

QTc: Corrected QT, QTd: QT dispersion, Tp-e: T peak to T end interval.

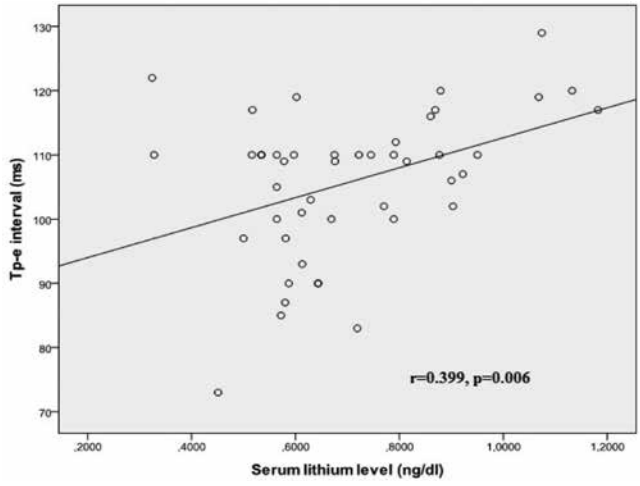

Figure 1. Correlation between Tp-e interval and serum lithium levels.

Table 4. Multivariate linear regression analysis to demonstrate independent predictors of increased Tp-e interval and Tp-e/QT ratio

	Tp-e interval		Tp-e/QT ratio	
	β coefficient	p	β coefficient	p
Age	0.056	0.694	0.033	0.830
Daily lithium dose	-0.251	0.071	-0.101	0.510
Serum lithium level	0.398	0.007	0.261	0.098

Tp-e: T peak to T end interval.

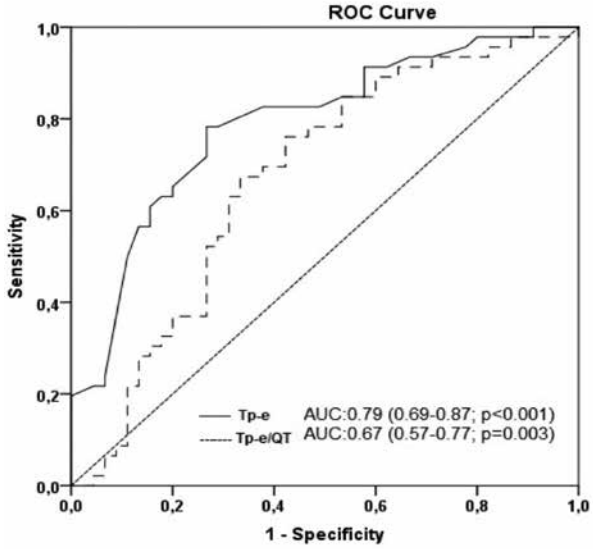

Figure 2. Identification of cut off values for Tp-e and Tp-e/QT in the study population via ROC curve analysis. AUC: Area under the curve, ROC: Receiver operating characteristic.

0.69-0.87; p< 0.001 and Tp-e/QT > 0.25; sensitivity, 67.0%; specificity, 64.0%; area under the curve, 0.67; 95% confidence interval, 0.57-0.77; p= 0.003; Figure 2).

DISCUSSION

In our study, we found that the QT, QTc, Tp-e interval, and Tp-e/QT ratio were significantly higher in the BD group than those in the control group. In addition, we found that increased Tp-e interval was significantly correlated to the serum lithium levels. We also found that increased serum lithium level was an independent predictor of prolonged Tp-e interval.

BD is a mood disorder characterized by episodes of mania and depression. Lithium is the first line of treatment for this disorder. The serum lithium levels must be monitored to maintain them within the normal range because the therapeutic range is quite narrow (0.6-1.2 mEq/L)[16]. Approximately 20%-30% of patients treated with lithium may suffer from cardiac side effects such as arrhythmias[17]. In addition, many of these arrhythmias, including sinus node dysfunctions, atrial flutter, atrioventricular blocks, and Brugada-type electrocardiographic changes, were observed within the therapeutic dose range of lithium treatment[4,7,13]. The electrical instability induced by lithium treatment may be the cause of arrhythmias even when lithium levels are in the therapeutic range[18].

VR may be assessed based on the QT interval, QTc interval, and dispersion of VR; these values are associated with an increased risk of cardiac arrhythmias[10,11,19]. The frequent use of lithium has helped us determine the side-effect mechanisms. Previous studies have suggested a mechanism of dose-dependent inhibition of the myocyte voltage-gated sodium channels, which decreases intracellular potassium, thereby causing electrical instability in the ventricles[12,20]. However, the mechanisms by which lithium affects VR parameters have not been clarified. Experimental studies have shown that lithium changes cations in the heart cells and causes intracellular metabolic changes. These changes include intracellular potassium depletion, which can be one of the mechanisms that cause Twave changes[4,21]. This finding supports the idea that depletion of intracellular potassium may lead to changes in lithium-related T wave and impaired distribution of VR. The intracellular loss of potassium may not necessarily lead to extracellular hypokalemia. It is possible that there is no clinical hypokalemia in patients under lithium therapy. This may explain the normality of potassium levels in our patients, regardless of the lithium level. In our study, there were no significant differences in serum potassium levels between the lithium-treated group and the control group.

Few clinical studies have investigated the relationship between lithium administration and QT prolongation[3,22]. A study by Altinbas et al. reported that BD patients using lithium had QT and QTc intervals comparable to those of healthy controls[23]. Kurt et al. found that QTc minimum was higher in the lithium and valproate groups than that in the control group, whereas the QTc dispersion values in the lithium and valproate group were significantly lower than those in the control group[24]. Bucht et al. studied the ECGs of 53 consecutive patients on lithium therapy and concluded that QTc changed after treatment initiation[25]. However, there are some methodological differences between their study and ours. First, they did not evaluate the correlation between QTc and serum lithium levels. Second, we excluded patients who were treated with thioridazine, pimozide, and tricyclic antidepressants. These well-known drugs have been proven to prolong QT interval[26]. Chen et al. did not demonstrate significant differences between serum lithium levels and QTc duration in their study[27]. In another study, both QT and QTc intervals were higher in patients with over-range lithium levels than in those without over-range lithium levels[28]. In our study, although lithium levels were in the therapeutic range, QT and QTc intervals were significantly higher in the BD group than in the control group, and the QTmax and QTmin intervals were similar between the groups. These findings suggest that the effects of lithium on VR are independent of overdose.

The Tp-e interval is a well-known marker of increased dispersion of VR. This marker is also used as an electrocardiographic

index of ventricular arrhythmogenesis and sudden cardiac death. Previous studies have shown that the prolongation of the Tp-e interval is associated with increased mortality[6,19]. Altinbas et al. found a greater Tp-e interval in patients with BD than in healthy volunteers[22]. However, in this study, the correlation between serum lithium concentration and Tp-e/QT ratio was not evaluated. In our study, Tp-e interval and Tp-e/QT ratio were significantly higher in the BD group than in the control group. These results were also correlated to serum lithium levels. The Tp-e interval is more valuable in predicting serum lithium levels.

Serious arrhythmias can be reported in patients under lithium therapy. This study may contribute to a greater understanding of the risk of ventricular arrhythmias established via the measurement of the Tp-e interval, which is obtained by ECG. BD patients who have a prolonged Tp-e interval should be observed closely, and their serum lithium levels should be measured frequently.

Limitations

One of the limitations of this study was the relatively small number of participants, which may have negatively affected the statistical power of the study. Long-term prospective studies are needed to fully determine whether the prolonged Tp-e interval observed in BD patients using lithium has any clinical consequences in terms of arrhythmia.

CONCLUSION

Our study revealed that the Tp-e interval was prolonged in BD patients under lithium therapy. Our results also indicated that Tp-e interval was significantly correlated with the serum lithium levels of BD patients.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: CZ, KK, KK

Analysis/Interpretation: KK

Data Acquisition: OK, GB, MS

Writting: CZ, KK

Critical Revision: KK, OK, GB, MS

Final Approval: All of authors

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