



## Electrocardiography changes in bipolar patients during long-term lithium monotherapy



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### ARTICLE INFO

#### Article history:

Received 4 February 2014

Revised 1 July 2014

Accepted 2 July 2014

#### Keywords:

Bipolar disorder

Lithium

ECG

QT interval

Arrhythmia

### ABSTRACT

**Objective:** Cardiovascular side effects of lithium have been reported to occur mainly at higher-than-therapeutic serum levels. We aimed to investigate the impact of the long-term lithium use on electrocardiogram (ECG) parameters in association with the serum levels in patients with bipolar disorder (BD) and in healthy controls (HCs) serving as the reference group.

**Methods:** The study sample consisted of 53 euthymic BD type I patients on lithium monotherapy at therapeutic serum levels ( $M=0.76$ ,  $S.D.=0.14$ ,  $range=0.41-1.09$  mmol/l) for at least 12 months and 45 HCs. A 12-lead surface ECG was obtained from all participants at resting state for at least half an hour for 5-min recording. Heart-rate, Pmax, Pmin, QRS interval, QT dispersion, QT dispersion ratio (QTdR) and Tpeak-to-end interval (TpTe) were measured.

**Results:** Regression analyses revealed that QTdR ( $B=14.17$ ,  $P=.001$ ), TpTe ( $B=18.38$ ,  $P<.001$ ), Pmax ( $B=17.84$ ,  $P<.001$ ) and Pmin ( $B=25.10$ ,  $P<.001$ ) were increased in BD patients who were on chronic lithium treatment than in HCs after controlling for age, sex and strict Bonferroni correction for multiple testing. There were no associations between serum lithium levels and ECG parameters.

**Conclusion:** Our findings suggest that the use of lithium is associated with both atrial and ventricular electrical instability, even when lithium levels are in the therapeutic range.

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Lithium is still considered as a first-line medication in the treatment of bipolar disorders (BDs) [1]. However, its narrow therapeutic range leading to increased risk of intoxications limits the widespread use of lithium in clinical practice [2]. Besides dermatologic, endocrinological, renal and cognitive side effects [3], lithium use has also been associated with cardiovascular side effects, which emerge mainly at higher-than-therapeutic levels. Various electrocardiography (ECG) changes such as sinus and atrioventricular node dysfunctions, complete blocks, junctional bradycardia, myocardial infarction, QT prolongation, and ST segment and T wave changes have been associated with lithium overdose [4–11]. Moreover, there are case reports showing that cardiac side effects might arise at therapeutic levels among patients who are on lithium treatment for long period of time or even with a single dose of lithium [12–15]. Possible mechanism of action for the cardiac side effects was proposed

to be related with lithium's influence on ion distribution involving competition with sodium, potassium, calcium and magnesium ions that all play important roles in cell membrane physiology.

Given this background, we aimed to investigate the impact of the long-term lithium use on ECG parameters in association with the serum levels in patients with BD and in healthy controls (HCs) serving as the reference group.

### 1. Methods

#### 1.1. Study sample

The study sample was consisted of 53 euthymic BD type I patients who were on lithium monotherapy with therapeutic serum levels ( $M=0.76$ ,  $S.D.=0.14$ ,  $range=0.41-1.09$  mmol/l) for at least 12 months and 45 HCs. Of 98 participants, 31 (58.5%) were females in the BD group and 20 (44.4%) were females in the HC group. Patients were recruited from Rasit Tahsin Mood Clinic of the Bakirkoy Research and Training Hospital for Psychiatry, Neurology, and Neurosurgery

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(RTMC). All patients were euthymic for at least 2 months, confirmed with the Young Mania Rating Scale (YMRS) and the 17-item Hamilton Depression Rating Scale (HAMD). Exclusion criteria for all patients were fulfilling the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for a mood episode, and a HAMD or a YMRS total score <7. Patients were diagnosed according to DSM-IV criteria and evaluation of standardized medical records as prescribed by the SKIP-TURK nationwide mood disorder follow-up program [16]. Medical and psychiatric histories were reviewed using the medical records of RTMC. The HC group consisted of individuals who were admitted to the Bakirkoy Sadi Konuk Training and Research Hospital Cardiology Outpatient Unit for checkup.

Bipolar patients diagnosed with thyroid disorders (e.g., hypothyroidism, hyperthyroidism) or cardiovascular disorders, (e.g., valvular heart diseases, cardiomyopathies, congenital heart diseases, pulmonary diseases, pulmonary hypertension, acute coronary syndromes, heart failure, myocardial infarction, implanted permanent pacemaker/defibrillator, coronary artery bypass grafting before the initial start date of lithium treatment or currently treated with antiarrhythmic medications) and patients with electrolyte imbalance were excluded from the study.

Exclusion criteria for the HC group were nonreliable QRS and T waves on the ECG, nonsinus rhythm, paroxysmal atrial fibrillation, other rhythm-conduction disturbances, valvular heart diseases, thyroid disorders, cardiomyopathies, congenital heart diseases, pulmonary diseases, pulmonary hypertension, electrolyte disturbances, acute coronary syndromes, heart failure, history of myocardial infarction, implanted permanent pacemaker/defibrillator, history of coronary artery by-pass grafting, history of coronary interventions and antiarrhythmic drug therapy.

The Medical Ethics Committee of Bakirkoy Research and Training Hospital for Psychiatry, Neurology, and Neurosurgery approved the study protocol, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

### 1.2. Procedure

A 12-lead surface ECG with 50-mm/s paper speed was obtained from all participants in the supine position in daytime, resting state for at least half an hour, by Hewlett-Packard E-300 ECG machine for 5-min recording. All ECG measurements were performed with a magnifying glass and an ECG ruler. One observer made all measurements, and results were checked by another blind cardiologist. The heart rate (HR) was observed with monitoring the patient for 30 min, and the mean of the values was accepted as average HR. The onset of the P wave was determined as the point of the first visible upward of the trace from the bottom of the baseline for the positive waves and as the point of first downward departure from the top of the baseline for negative waves. The return to baseline was considered to be the end of the P wave. The Pmax was defined as the longest atrial conduction time measured from the 12 leads; and Pmin, as the shortest atrial conduction time. The QT interval was measured from the beginning of QRS to the end of T wave in each ECG lead. Return of the T wave to isoelectric line was defined as the end of the T wave. The QT interval should have been measurable in at least eight derivations and at least three QT intervals in a derivation. The longest (QTmax) and the shortest (QTmin) QT intervals were measured for all patients. QT interval measurements were rate-corrected with a modification of Bazett's formula (QTc). QT dispersion (QTd) was defined as the difference between QTmax and QTmin (QTd=QTmax–Qtmin). QT dispersion ratio (QTdR) was obtained by the formula QTd/RR (ms)×100. Tpeak-to-end interval (TpTe) was measured in every lead on which T wave was identified easily and variation seldom appeared. Blood was drawn in the morning approximately 12 h after

the last intake of the lithium capsules, and serum lithium level was measured.

### 1.3. Statistical analysis

STATA version 12.0 (STATA Corporation, College Station, TX, USA) was used to carry out the statistical analyses. Associations between the groups (HC and BD) and approximately normally distributed ECG parameters were expressed as unstandardized regression coefficients (B) with 95% confidence interval (95% CI) from multiple regression procedures with ECG parameters as dependent variables and dummy variables of the two groups as independent variables, with the HC group serving as reference. Additionally, regression analyses were conducted in order to evaluate the association between lithium levels and ECG parameters in patients with BD. The 'ROBUST' option in STATA was used to adjust estimates of standard errors in all regression analyses. In order to check the validity of our findings, we additionally applied the distribution-free method of bootstrapping to each regression analysis (with  $n=1000$  bootstrap resamples) [17]. As there were no marked differences from the bootstrap results, results from ordinary least squares regression analyses with robust standard errors were reported. All analyses were corrected for a priori selected confounders: age and sex. Between-group differences in age and sex were analyzed with  $t$  test and  $\chi^2$ , respectively. Two-sided statistical significance was set at  $P<.05$ . Each hypothesis was corrected using the Bonferroni procedure for multiple testing (adjusted  $P=.00625$ ).

## 2. Results

Mean age was 40.8 (S.D.=11.2) years in patients and 40.9 (S.D.=11.6) years in HCs. There were no statistically significant differences between groups in terms of sex ( $P=.17$ ) and age ( $P=.96$ ). QTdR, TpTe, Pmax and Pmin were higher in patients than in HCs after controlling for age, sex and Bonferroni correction for multiple testing (adjusted  $P=.00625$ ) (Table 1). Patients were on lithium for a mean period of 10.4 years (S.D.=5.8; range=1–28 years). Mean serum lithium level was 0.76 (S.D.=0.14) mmol/l (range=0.41–1.09). There were no associations between serum lithium levels and ECG parameters (Table 2). There were no participants with a cardiac abnormality that requires further treatment in BD and in HC groups.

## 3. Discussion

The present findings showing higher QTdR, TpTe, Pmax and Pmin in patients with BD compared to those in HCs suggest that the use of lithium might be associated with both atrial and ventricular electrical instability, even when lithium was used at therapeutic levels.

P wave represents the wave of depolarization spreading from the sinoatrial node throughout the atria and is an indicator of atrial depolarization. The P wave indices have received increased attention

**Table 1**  
The effect of lithium use on ECG parameters

	Unadjusted			Adjusted <sup>a</sup>		
	B	95% CI	P	B	95% CI	P
Heart rate	7.99	1.87 to 14.11	.01	7.59	1.41 to 13.77	.02
QTmax	12.97	–1.49 to 27.43	.08	13.74	–1.53 to 29.02	.08
QTmin	10.01	–4.25 to 24.28	.17	10.68	–4.07 to 25.44	.15
QTd	2.96	–1.69 to 7.61	.21	3.06	–1.72 to 7.83	.21
QTdR	14.53	6.57 to 22.50	<.001	14.17	6.28 to 22.07	.001
TpTe	17.93	11.84 to 24.02	<.001	18.38	12.42 to 24.35	<.001
Pmax	18.49	12.37 to 24.61	<.001	17.84	11.33 to 24.34	<.001
Pmin	25.49	19.23 to 31.75	<.001	25.10	18.79 to 31.42	<.001

Healthy controls served as the reference category.

<sup>a</sup> Adjusted for age and sex.

**Table 2**  
The association between plasma lithium levels and ECG parameters in bipolar patients

	Unadjusted			Adjusted <sup>a</sup>		
	B	95% CI	P	B	95% CI	P
Heart rate	16.02	−22.20 to 54.24	.40	20.27	−18.24 to 58.78	.29
QTmax	−27.56	−119.28 to 64.16	.55	−26.35	−119.63 to 66.93	.57
QTmin	−17.37	−106.89 to 72.15	.70	−18.90	−111.46 to 73.66	.68
QTd	−10.19	−41.88 to 21.50	.52	−7.44	−40.44 to 25.55	.65
QTdR	10.14	−47.42 to 67.70	.72	16.67	−42.28 to 75.63	.57
TpTe	4.35	−36.46 to 45.16	.83	5.62	−35.37 to 46.60	.78
Pmax	17.11	−34.43 to 68.66	.51	18.77	−30.77 to 68.30	.45
Pmin	−2.91	−52.20 to 46.37	.91	0.84	−49.96 to 51.64	.97

<sup>a</sup> Adjusted for age and sex.

in the last few years and were proposed as predictors for atrial fibrillation [18]. Given this background, the significant increase in Pmax and in Pmin in BD could be interpreted as disturbed electrical activity that might be related with the long-term lithium use considering the literature indicating disturbances such as sinus node dysfunctions, atrial flutter, the Brugada-type electrocardiographic changes and atrioventricular blocks during the long-term lithium treatment [8,10,12–14].

QT interval is an indicator of ventricular depolarization and repolarization, measured easily in daily clinical practice with the ECG. The clinical importance of QT interval variability is a topic of growing interest worldwide. The difference between the longest and the shortest QT intervals measured from a 12-lead standard ECG recording is defined as QTd [19]. QTd is a criterion pointing out the heterogeneity of myocardial repolarization and yet a potential prognostic tool for predicting ventricular arrhythmias and mortality. QTdR is defined as QTd divided by the cycle length (in other words, RR interval). It has been shown that QTdR is a better predictive tool than QTd for ventricular arrhythmias [20]. Moreover, increased QTdR suggests heterogeneity of ventricular repolarization, which may take part in ventricular arrhythmia development [21]. In addition, the other parameter that we found higher in patients with BD was TpTe, which is also proposed as an index to quantify increased ventricular repolarization dispersion and arrhythmia risk [22]. Although lithium influenced several ECG parameters, there were no participants with a cardiac abnormality requiring further treatment in the BD group. Therefore, it is difficult to clearly conclude about the clinical importance of these ECG changes. However, it is plausible to consider these changes as indicators of susceptibility to cardiovascular side effects and possible predictors for future arrhythmias.

There are numerous case reports showing the effects of lithium treatment on cardiac electrical activity both at toxic [4–11] and at therapeutic levels [12–14], including sinus node dysfunctions, atrial flutter, the Brugada-type electrocardiographic changes and atrioventricular blocks [8,10,12,23]. Although the working mechanism underlying lithium's cardiovascular side effects is not clear, Na-K pump blockade in cell membrane is thought to play a role [4,14,24]. Additionally, dose-dependent inhibition of voltage-gated sodium channels via a multi-ion mechanism may influence the myocardial conduction velocity [4,24,25]. Given the crucial role of cardiac sodium channels in sinus nodal pacemaker activity, lithium may cause a sinus node dysfunction through the failure of impulse generation or conduction into the adjacent atrial myocardium [24,26]. The decrease in adrenergic response and the complex interaction between sodium and pacemaker (L-type calcium and acetylcholine-gated potassium) channels were also deemed responsible [10,24]. Furthermore, Na-K exchange blockade in cell membrane may lead to intracellular hypokalemia and extracellular hyperkalemia, which are considered as a risk factor for arrhythmias [26]. However, all these changes in cardiac electrical activity generally occur at toxic lithium levels rather than at therapeutic levels [4,14].

The present study investigating the impact of lithium at therapeutic levels on ECG parameters sheds some light on this important topic. However, there are several limitations that need to be considered interpreting the present findings. Recently, ion channel gene polymorphisms were attributed to the etiology of BD [27]. Therefore, we cannot state that the differences in ECG parameters are solely due to the lithium use. Indeed, some of these changes might also be attributed to the pathogenesis of BD. In order to verify this theory, a sample of unmedicated euthymic patients with BD is required. Additionally, our sample consisted only of patients who were on lithium for long period of time; therefore, it should be taken into account that the lithium's impact on ECG parameters may be a late side effect of lithium rather than an acute side effect [8,12]. Moreover, it should be considered that the findings of this present cross-sectional study do not imply causality, and the relatively small sample size stands as a possible limitation.

Overall, our findings suggest that the use of lithium is associated with both atrial and ventricular electrical instability, even when lithium is used in the therapeutic range. Prospective large sample-sized studies including unmedicated BD patients that measure ECG parameters before and after the initiation of lithium treatment are required to confirm the clinical importance of these findings.

### Acknowledgments

We would like to thank Prof. Willem Nolen who kindly reviewed the article and shared his comments on the article. S.G. would like to thank the support of the European Community's Seventh Framework Programme under grant agreement no. HEALTH-F2-2009-241909 (Project EU-GEI).

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