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Short Communication

Electrocardiographic Changes during Initiation of Lithium Augmentation of Antidepressant Pharmacotherapy

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ABSTRACT

Purpose/Background: Lithium augmentation (LA) of antidepressants represents a common strategy to overcome treatment-resistance in patients with major depressive disorder (MDD). The use of lithium has been associated with cardiovascular side effects such as QTc prolongation and tachyarrhythmia. While previous studies investigated monotherapy with lithium, the aim of this study is to investigate electrocardiographic changes in LA.

Methods/Procedures: A 12-lead surface electrocardiogram (ECG) was obtained from 38 patients with MDD before and during LA. Changes in heart rate (HR), PQ, QRS and QTc interval, QT dispersion, ST segment, and T and U wave alterations were analyzed using a linear mixed model.

Findings/Results: The ECG readings of 33 patients were evaluated. LA was not significantly associated with changes in HR, QTc, PQ, or QRS interval. We found a significant decrease in QT dispersion. These results were independent of sex, age, stable comedication, and comorbidities. During LA, we observed nine cases of T wave alterations, and two cases of new U waves.

Conclusions: Our data provides no evidence for serious ECG abnormalities at therapeutic serum lithium levels in patients treated with LA. In particular, we did not find evidence for QTc time lengthening or tachyarrhythmia such as torsades des pointes. The recommended intervals for ECG checks should be considered to detect long-term effects of LA.

Keywords: Depression treatment, pharmacodynamics, treatment-resistant depression, Lithium augmentation, electrocardiography

1. Introduction

As a monotherapy, lithium has been widely used for many decades as a maintenance treatment for bipolar disorder and in the acute treatment of mania. Following the most popular guidelines, lithium augmentation (LA) of antidepressants is also a recommended and effective strategy to overcome treatment resistance in patients with major depressive disorder (MDD) [1,2]. Typically, lithium is administrated in the form of carbonate, citrate or -acetate. The monovalent lithium cation is not biotransformable in the body and is eliminated renally. An individually adjusted dosage is necessary to reach the recommended serum lithium levels for LA (0.5−0.8 mmol/l; whereby an overall therapeutic range of 0.4−1.2 mmol/l exists). At serum levels above the therapeutic range, especially ≥ 1.5 mmol/l, cardiotoxic side effects have been described: These can range from sinoatrial block [3], profound sinus bradycardia [4], sinus arrest and QT prolongation with the risk of severe ventricular tachyarrhythmias [5] to asystole [6]. Previous studies of the impact of lithium on the heart have suggested a disturbed cell membrane physiology in cardiomyocytes with a decreased flow of sodium inward and a decreased potassium outward, leading to inhomogeneous and prolonged de- and repolarization of both atria and ventricles [7-10].

When therapeutic serum levels are achieved, the most frequently reported changes of the electrocardiogram (ECG) include T-wave alterations and a decrease in heart rate or sinoatrial block [8]. No evidence of QTc lengthening has been reported [11,12]. Monoadministration of lithium within therapeutic serum levels is not known to cause serious ECG changes [8]. Monotherapy of depression using antidepressants, though, is associated with changes in the QT interval. However, the risks differ depending on the antidepressant class and the specific agents [13,14]. Comparing the frequency of cardiovascular adverse drug reactions defined according to the “AMSP study guidelines” [15]selective serotonin reuptake inhibitors (SSRIs) show a significantly lower risk than tricyclic antidepressants (TCAs) [16]. The combination of an antipsychotic agent with an antidepressant or with lithium is also known to cause significant QTc prolongation [17].

To the best of our knowledge, to date, no study has investigated the impact of LA on ECG changes. To bridge this clinically relevant knowledge gap, the aim of this study is to investigate changes in ECG during LA in patients with MDD.

Materials and Methods

Patients

The study population is a subsample of a naturalistic prospective multicenter cohort study investigating the treatment response and side effects of LA (initial trial registration: EudraCT Registration No. 2008-004182-26; further trial registration: German Clinical Trials Register No. DRKS00026205). The inclusion criteria were: with a diagnosis of unipolar depression, at least 18 years of age, insufficient response to at least one antidepressant pre-treatment over at least four weeks, clinical indication for LA, Hamilton Depression Rating Scale score ≥ 12 [18], and written informed consent. Furthermore, patients were only included when comedication was stable.

Exclusion criteria were: contraindication for LA, depressive syndrome due to another somatic or psychiatric diagnosis, a diagnosis of dementia or another severe cognitive impairment, substance abuse disorder with fewer than six months of abstinence, antisocial personality disorder, missing or incomplete ECG files, or a time interval of fewer than 10 days between LA treatment initiation and follow-up ECG.

Patients were recruited between 2008 and December 2019 in 12 psychiatric departments of the Berlin Research Network on Depression, Berlin, Germany.

Measurements

Somatic comorbidities: The severity of somatic comorbidity was assessed according to the updated version of the Charlson Comorbidity Index [19].

Comedication: Antidepressants and other stable concomitant medications as well as pro re nata (PRN) medication were recorded with active ingredient and dosage. In regard to potentially lithium level-altering concomitant medication we defined these drugs according to Scherf-Clavel et al. [20]. The number of patients receiving at least one potentially lithium level-altering concomitant medication at baseline is provided in Table 1. In order to operationalize the risk of QTc lengthening and and torsades des pointes (TdP), we used a comedication risk score as published by Wenzel-Seifert et al. [21]. As recommended, the score was updated using the online tool “CredibleMeds” from the Arizona Center for Education and Research on Therapeutics [22]. This comedication risk score was determined for each patient. If patients received medications in addition to their lithium and antidepressant, the comedication risk score was taken from to the active ingredient with the highest score. All antidepressants were assigned among the following classes: SSRI, TCA, serotonin and norepinephrine reuptake inhibitors (SNRI), mirtazapine and monoamine oxidase inhibitors (MAO-I).

Lithium level: *All patients received lithium as carbonate and the dose was determined by their serum levels, with the aim of reaching a therapeutic concentration of 0.5–0.8 mmol/l*. Lithium levels were measured weekly and as through levels (i.e., immediately before the next intake). For the statistical analysis, the last lithium level before follow-up ECG was used. The time frame from initiation of LA treatment to follow-up ECG is defined as the duration of lithium administration in days.

ECG analysis**:** A 12-lead surface ECG with 50mm/s paper speed was obtained at resting state. Analyses were performed by a blinded, experienced observer and reviewed by a second reader. Using a commercial ECG lineal for manual evaluation, the following parameters were measured: heart rate and rhythm, cardiac axis, PQ interval, QRS interval, QT interval, QT dispersion, ST segment, and T wave and U-wave alterations. The evaluation was done manually given that performance characteristics are considered to be at least equivalent to automatic ECG analysis [23]. To assess heart rate, we measured all RR intervals and calculated an average value. The QT interval was measured as previously described by Lepeschkin and Surawicz [24]. To calculate the QTc time we chose the longest interval and corrected it for heartrate using the Bazett formula [25]. QT dispersion was defined as the difference between the shortest and the longest measured QT intervals within the recorded time. We defined relevant T and U wave alterations according to the Minnesota Code Classification System for Electrocardiographic Findings [26]. One single ECG was evaluated per time point as per clinical routine.

Statistical analysis

We used a linear mixed model for statistical analysis to investigate the effect of LA (time) as an explanatory factor for changes in ECG parameters. We performed separate analyses for each ECG parameter (heart rate, PQ time, QRS time, QTc time, and QT dispersion) as the dependent variable. Linear mixed-effects models have the advantage of allowing the investigation of variability between patients (heterogeneity) and simultaneously adjusting for within-subject correlation. In the present analysis, random effects were permitted for the intercepts. We screened for the following variables as potential confounders: sex, age, antidepressant class, comedication risk score, Charlson Comorbidity Index, duration of lithium administration, PRN medication, and last lithium level. The threshold for entering a confounder into the model was a p-value of less than 0.1. Model regression coefficients are reported together with their standard error estimates and a 95% confidence interval (CI). The Kolmogorov-Smirnov test was used to verify the normal distributions of the sample. We applied McNemar's, t- and Wilcoxon signed-rank tests where appropriate. We used SAS software, version 9.4.

to perform the linear mixed model analysis. The significance level was set at 0.05 for all analyses. Descriptive statistics were completed using IBM SPSS Statistics (version 26).

2. Results

While 38 patients met inclusion criteria, five dropped out due to a comedication change after initiating LA treatment (dose escalation of antidepressant and additional antipsychotic; switch of antidepressant from TCA to mirtazapine; switch of antidepressant from SNRI to TCA; additional SSRI; and switch of antidepressant from SSRI to bupropion). Twenty-two of the remaining 33 participants were female, and the age was 55.1 ± 13.9 years (mean ± standard deviation; minimum age 32 years, maximum age 78 years). Other patient characteristics are summarized in Table 1.

Table 1

Characteristics of study population at baseline

Parameter	*n*	*%*	*M*	*SD*
Duration of lithium administration [days]			32.27	15.57
Time between last lithium level and ECG [days]			9.16	10.22
Patients receiving at least one potentially lithium level-altering concomitant medication [number] [a]	5	15.15		
Antidepressant class				
- SSRI	16	48.48		
- SNRI	10	30.30		
- Mirtazapine	4	12.12		
- TCA	2	6.06		
- MAO-I	1	3.04		
Last Lithium level before follow-up ECG [mmol/l]			0.75	0.27
Charlson Comorbidity Index			0.21	0.49
Comedication risk score			1.18	0.81
Age [years]			55.10	13.90
Sex				
- Female	21	63.64		
- Male	12	36.36		
- total	33	100		

Note. SSRI = Serotonin Reuptake Inhibitors; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; TCA = Tricyclic Antidepressant; MAO-I = Mono Amine Oxidase Inhibitor (Tranylcypromine).

[a] potentially lithium level-altering concomitant medication: diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin 1 receptor (AT1) antagonists, and non-steroidal anti-inflammatory drugs

During the treatment, no serious cardiac side effects or potentially life-threatening arrhythmias occurred. In regard to other ECG changes, we found nine cases with changes in T-wave morphology occurring as new isoelectric T waves. In two cases, we observed new U waves. There were no changes in ST interval and no newly occurring atrioventricular or bundle blocks. The preexisting first-degree atrioventricular block of one patient remained unchanged.

Screening analysis of the linear mixed model revealed sex to be a confounder for heart rate, age as a confounder for PQ time, and AD class to be a confounder for QTc time. Sex, age, and AD class were entered into the model as confounding covariates for the ECG parameters.

The results of ECG analysis at both timepoints are shown in Table 2. Between baseline and follow-up we found no significant changes in rhythm, heart rate (estimated differences: 1.24 bpm; 95%-CI: -2.96−5.45; $F_{1.32} = 0.36$; $p = 0.55$), PQ time (estimated differences: 2.16 ms; 95%-CI: -3.67−7.99; $F_{1.31} = 0.57$; $p = 0.46$), QRS time (estimated differences: 1.82 ms; 95%-CI: -1.78−5.41; $F_{1.32} = 1.06$; $p = 0.31$) and QTc time (estimated differences: 7.93 ms; 95%-CI: -1.64−17.49; $F_{1.32} = 2.85$; $p = 0.10$). The QT dispersion decreased significantly after treatment initiation of LA (estimated differences: 8.85 ms; 95%-CI: 0.74−13.26; $F_{1.32} = 5.19$; $p = 0.03$).

Regarding the confounding covariates in the analyses described above, we found a significant negative effect of male gender on heart rate ($p < 0.05$). Age was significantly associated with a longer PQ time ($p < 0.05$) and the AD class TCA was significantly associated with a longer QTc time when compared to MAO-I, SSRI, SNRI and mirtazapine ($p < 0.05$).

Table 2

ECG parameters before (Baseline) and after (Follow-up) treatment initiation of lithium augmentation of antidepressants

ECG Parameter	Baseline [a]			Follow-up [a]			*p**
	n	*M*	*SD*	*n*	*M*	*SD*	
Rhythm							
- Sinus rhythm	32			32			1.00
- Atrial fibrillation	1			1			1.00
AV block	1			1			1.00
Heart rate (bpm)		77.70	9.79		76.46	12.04	0.55
PQ time		161.56	37.47		159.41	38.83	0.46

QRS time (ms)		80.30	13.80		78.49	10.35	0.28
QT max (ms)		360.91	28.21		356.36	30.80	0.30
QTc time (ms)		405.62	28.10		397.69	20.80	0.10
QT dispersion (ms)		22.80	14.9		15.80	15.70	0.03
U wave	0			2			0.50
Isoelectric T wave	11			20			<0.01

Note. AV block = atrioventricular block

[a] n = 33

* p-value, result of t test or Wilcoxon signed-rank test for metric parameters; McNemar test for categorical parameters

3. Discussion

This is the first study evaluating ECG changes in patients treated with LA. We found no abnormalities in rhythm, heart rate, PQ time, QRS time, or QTc time after treatment initiation of LA, but a significant decrease in QT dispersion. Furthermore, we found nine new isoelectric T waves and new U waves in two cases. We did not observe any serious cardiac side effects or potentially life-threatening arrhythmias.

Besides lithium intoxications, ECG changes have also been described in long-term or chronic lithium treatment at therapeutic serum levels: Four prospective studies investigating lithium monotherapy reported decreased heartrate or T-wave changes, occurring as flattening, inversion, or isoelectric T waves [12,27-29]. Demers and Heninger found T-wave depressions at some timepoint in all of their nine patients studied [29]. Bucht et al. investigated 53 patients and recorded ECG prior to and at four and 12 months after treatment initiation with lithium. T-wave flattening, followed by a decrease in heart rate, were the most frequently-observed changes [12]. While changes in T-wave morphology seem to be a common and stable finding, a decrease in heart rate during lithium administration has been reported less frequently [27,28]. In line with evidence from monotherapy literature, we also found newly-occurring isoelectric T waves in nine cases but no significant decrease in heart rate. A decreased sodium inward flow and a decreased potassium outward flow are considered as lithium-induced mechanisms leading to T-wave flattening, similar to hypokalemia, while serum potassium levels are normal [7,30]. T-wave alterations are often reversible after treatment discontinuation and are discussed to be without clinical significance in lithium treatment [12,27,30]. However, independent from pharmacotherapy, T-wave alterations are associated with a higher risk for tachyarrhythmia in patients with heart diseases [31]. LA

might be administered with caution, and routine check-ups by a cardiologist might be considered more frequently in this at-risk population.

In line with previous studies investigating lithium monotherapy [11,12,27-29] QTc time did not increase during LA in our study. The univariate analysis showed a significant decrease in QTc time, whereas multivariate analysis yielded no significant changes. This is particularly interesting since one would expect prolongation of the QTc interval due to a combination of lithium with potential QTc time lengthening antidepressants. Depending on the specific drugs and especially on the corresponding dosage, the risk of QTc lengthening varies [13,14]. In general, however, newer antidepressants such as SSRIs seem to be associated with lower risk compared to TCAs [14]. It is relevant to note that TCAs were only administered in two cases and the recommended dosage ranges were not exceeded in any case. The risk of QTc prolongation or TdP, which is inherent to antidepressant medication, can therefore be considered as relatively low in our study population.

In line with the previous studies reviewed above, we observed no severe tachyarrhythmia or TdP in our study population.

While it seems that lithium monotherapy does not lead to QTc time lengthening, studies investigating cardiac side effects are increasingly focusing on QT dispersion. QT dispersion represents the heterogeneity state of ventricular repolarization. A QT dispersion > 58 ms is considered to be associated with a higher risk of cardiovascular mortality in healthy individuals [32].

Two studies found a significant association between lithium use and increased QT dispersion compared to healthy controls[11,28]. However, the explanatory power of these studies is significantly limited by the fact that the authors did not perform longitudinal studies [11,28], did not consider current use of lithium, lithium levels and depressive symptoms at the time of the ECG [11], or compared euthymic patients with healthy controls [28].

In contrast to the mentioned studies, we found a significant decrease in QT dispersion. It should be noted that in our study QT dispersion showed inconspicuous values at both timepoints (treatment with AD/LA), that did not differ from what is known of healthy individuals [32].

The observed decrease in QT dispersion during LA may indicate a more homogeneous repolarization of the myocardium. It seems possible that this effect is an expression of a decrease in depressive symptoms, whereby we propose the following mechanism as an explanation. A study with 50 newly diagnosed patients with unipolar depression and without antidepressant pharmacotherapy or other potential ECG-changing medication found increased QT dispersion compared to age- and sex-matched

healthy controls [33] presumably due to an elevated sympathetic tone. The decrease of QT dispersion in our study population may indicate the efficacy of antidepressant treatment using LA, leading to a normalization of parasympathetic tone. While Reilly et al. [11] do not make any statements about the severity of psychiatric symptoms at the time of the ECG, Altinbas et al. [28] explicitly examined euthymic patients. These differences in study populations make a direct comparison of alterations in QT dispersion difficult.

The strengths of our study are the longitudinal design, the control for lithium levels and the attention paid to somatic comorbidities as well as concomitant medications, especially antidepressants, to investigate the impact of LA on ECG parameters. In contrast, the lack of a control group reflects the most important limitation of our study. To this extent, we cannot conclude that the observed findings are specific for LA compared to antidepressant monotherapy. Furthermore, given the observation period of a maximum of three months, no statements can be made regarding the long-term effects of LA. Other limitations include the relatively small sample size, the lack of long-term ECG data to detect paroxysmal arrhythmia, and the fact that ECG analyses were not the primary endpoint of the study.

In conclusion, our data provides no evidence of serious ECG abnormalities under therapeutic serum lithium levels in patients treated with LA. In particular, we did not find evidence for QTc time lengthening or tachyarrhythmias such as TdP. The recommended intervals for ECG checks (usually annually after the first check following treatment initiation) should be considered to detect long-term effects of LA. Clinical studies solely investigating the side effects of ECG changes are still missing and reflects an area for future investigation.

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