IS THERE ANY RELATIONSHIP BETWEEN LITHIUM-INDUCED QT PROLONGATION AND PLASMA OR ERYTHROCYTE CONCENTRATION OF LITHIUM?

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ABSTRACT

This study was designed to find possible relationship between QTc prolongation and erythrocyte or plasma lithium concentrations. Fifty-six patients with bipolar disorder entered this case- control study. Subjects were between 17 to 63 years of age and were receiving lithium alone, or lithium plus haloperidol or lithium plus thioridazine. The exclusion criteria were past history of cardiovascular, hepatic, renal or metabolic disorders or using other medications known to cause rhythm disturbances. The case group included males with QTc≥ 450ms and females with QTc≥470ms while the control group included males and females with QTc<450 and QTc< 470ms, respectively. Serum sodium and potassium levels, erythrocyte and plasma lithium concentrations as well as lithium ratio were determined for all subjects and compared between the case and control groups by independent sample t-test. The mean of these levels were not different between the case and control groups. Additionally, no correlations were found between QTc and erythrocyte or plasma lithium concentration, lithium ratio, serum sodium or potassium levels. Analyzing the data for patients treated with lithium alone showed no significant correlations between QTc prolongation and erythrocyte or plasma lithium concentration, lithium ratio or serum potassium level. However, a significant correlation was found between serum sodium concentration and QTc prolongation. It should be noted that QTc prolongation occurred six times more in patients who were taking thioridazine and lithium concomitantly. This study noted no influence of sex or co-administration of haloperidol with lithium on QTc prolongation.

It is concluded that plasma or erythrocyte lithium levels may not be able to predict QTc prolongation and its consequences.

Keywords: Lithium, Erythrocyte lithium concentration, Plasma lithium concentration, Lithium ratio, QTc prolongation

INTRODUCTION

It has been identified that psychiatric patients are at risk for cardiovascular problems (1) and the mortality due to cardiovascular diseases in bipolar patients is much higher than in the general population (2). It has been suggested that cardiac side effects of drugs affect this mortality (3). Lithium (Li), a valuable mood-stabilizer, may cause several electrocardiographic (ECG) changes such as T-wave depression, isoelectricity or inversion in patients treating with this drug. Reversible sinus node dysfunction, atrioventricular (AV) node dissociation, AV block, junctional rhythm and premature ventricular contraction are rare adverse drug reactions of Li and may even occur at therapeutic serum Li concentrations (4). The QTc interval is a heart rate-corrected value that shows the total time of ventricular electrical activity. The Committee for Proprietary Medicinal Products has defined QTc values over 470 and 450 ms in females and males respectively as prolonged QTc. This committee considers QTc less than 450 and between 450 and 470 ms as normal and borderline, respectively, in females. Whereas QTc values of less than 430 and between 430 and 450ms are considered normal and borderline, respectively, in males (5).

Some psychotropic drugs such as Li, tricyclic antidepressants and some antipsychotic medications may prolong this interval and predispose patients to torsade de pointes ventricular tachycardia (6).

Several studies have shown that intracellular

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lithium level in comparison with plasma lithium concentration (PLC) has a better relationship with some Li-induced adverse effects such as renal concentrating defect, dyskinesia and dystonia. Erythrocyte lithium concentration (ELC) has been used as an indicator of intracellular level of this cation and the ratio of ELC over PLC has been termed as lithium ratio (LR) (7, 8). This study was designed to find possible relationship between QTc prolongation and ELC, PLC or LR.

MATERIALS AND METHODS

Patients with bipolar disorder according to DSM-IV criteria, who were admitted at Roozbeh Mental Health Hospital and were on lithium carbonate entered this case-control study without any change in its dosage for at least 7 days. Subjects were receiving either Li alone, or Li and thioridazine, or Li and haloperidol.

According to the patients' records and hospital routine evaluations including ECG, liver transaminases and alkaline phosphatase, serum creatinine and blood urea nitrogen, serum sodium, potassium, magnesium, and calcium, none of the subjects had a past history of cardiovascular, hepatic or renal diseases or metabolic/electrolyte disorders known to cause rhythm disturbances or receiving other medications that are known to affect QTc**.** Pregnant and nursing women and substance abusers were also excluded from this research. All patients/guardians gave informed consent. This study was approved by Ethics Review Committee of Tehran University of Medical Sciences.

The case group consisted of patients on lithium with QTc≥ 450ms for males and ≥470ms for females and the control group included males and females on Li with QTc<450 and QTc< 470ms, respectively.

Blood samples were collected 12±0.5h after the last dose of Li administration. Erythrocyte and plasma lithium concentrations of all subjects were measured by atomic absorption spectrophotometer. A direct method of ELC measurement was used in this study (9). Blood samples were analyzed for serum potassium (K) and sodium (Na) levels by flame-photometer.

ECGs were obtained in the supine position and analyzed by a cardiologist who was not aware of the hypothesis of this study, patients' status and treatment regimens. The QTc interval was calculated by the Bazzett formula (10).

Data were analyzed by the SPSS version 11 statistical package. The distribution of PLC, ELC and LR were found to be consistent with a Gaussian distribution. Therefore, comparisons of the ELC, PLC and LR between the case and control groups were made by independent sample t-test.

RESULTS

Fifty-six patients (40 males and 16 females) on Li alone, Li plus thioridazine or Li plus haloperodol enrolled in this study. Fifteen patients (10 males and 5 females) with the mean age of 33.13±9.84 years entered the case group. Control group consisted of 41 subjects (30 males and 11 females) whose mean ages were 35.71±11.52 years. There was no significant difference in age (P=0.45) between the cases and controls.

The mean PLC in the cases was 0.45±0.22 meq/L which did not differ significantly from that of the controls (0.52 ±0.26 meq/L) (P=0.29). The mean of ELC, LR and total Li daily dose in the case group were 0.18±0.15meq/L, 0.53±0.52, and 1130.00±246.26mg/d, respectively and were lower than those values in the control group (0.29±0.21meq/L, 0.62±0.36and 1181.25±252.34 mg/d, respectively). However, the mean differences were not statistically significant (P=0.08, 0.50 and 0.50 respectively). Serum K and Na levels of all patients were within normal limit and did not differ between the control and case groups (For K, 4.17± 0.40meq/L and 4.21±0.46meq/L, respectively (P = 0.72); for Na, 139.75 ± 2.20meq/L and 140.73± 2.31meq/L, respectively (P=0.20). These results are summarized in Table 1.

As shown in table 2, in this study no relationship were found between QTc and ELC, PLC, LR, Li daily dose, age, serum K or serum Na levels (P= 0.10, 0.96, 0.22, 0.81, 0.70, 0.97 and 0.10 respectively).QTc prolongation occurred 6 times more in patients who were taking thioridazine and Li concomitantly (OR=6.00, 95%CI= 1.39~25.86). However, no effect was found on QTc prolongation when haloperidol was concomitantly administered with Li. Additionally, sex did not affect QTc prolongation significantly.

When the patients using thioridazine concomitantly with Li were excluded from the analysis, 36 subjects (27 males and 9 females) were in the control group and the case group had 9 patients (6 males and 3 females). These subjects were treating with Li alone or with Li plus haloperidol. The mean age of patients was not significantly different (P=0.7) between controls (35.13±11.10 years) and case groups (33.55±10.55 years). As shown in table 3, the mean of PLC, ELC, LR, total Li daily doses and serum K and Na concentrations are not considerably different between two groups. No correlations were found between QTc and ELC, PLC, LR, Li daily dose, age or serum K and Na levels (P= 0.12, 0.98, 0.46, 0.89, 0.86, 0.79 and 0.14, respectively). The Pearson correlations and P values are shown in table 4. Gender or co-administration of haloperidol with Li had no influence on QTc prolongation in patients treated with Li alone or Li plus haloperidol.

Table 1. Characteristics of patients on Li alone or Li+thioridazine or Li+haloperidol in the case and control groups

Parameter	Case group[1]	Control group[1]	P Value
Age (Years)	33.13±9.84	35.71±11.52	0.45
PLC[2](meq/L)	0.45± 0.22	0.52± 0.26	0.29
ELC[3](meq/L)	0.18± 0.15	0.29± 0.21	0.08
LR[4]	0.53± 0.52	0.62± 0.36	0.50
Li daily dose (mg)	1130.00± 246.26	1181.25± 252.34	0.50
Sr K[5] (meq/L)	4.21± 0.46	4.17± 0.40	0.72
Sr Na[6] (meq/L)	140.73± 2.31	139.75±2.20	0.20

[1] Values are presented as Mean± SD; [2] Plasma Lithium Concentration; [3] Erythrocyte Lithium Concentration; [4] Lithium Ratio; [5] Serum K Concentration; [6] Serum Na Concentration

Table 2. Correlation analysis between QTc and PLC, ELC, LR, Li daily dose, SrK in patients treating with Li alone, Li+thioridazine or Li+haloperidol

Paremeter	Pearson correlation	P value
PLC[1] (meq/L)	-0.01	0.96
ELC[2] (meq/L)	-0.22	0.10
LR[3]	-0.17	0.22
Li daily dose(mg)	0.03	0.81
Age(years)	-0.05	0.70
Sr K[4] (meq/L)	0.01	0.97
Sr Na[5] (meq/L)	0.22	0.10

[1]Plasma Lithium Concentration; [2] Erythrocyte Lithium Concentration; [3] Lithium Ratio; [4]Serum K Concentration; [5]Serum Na Concentration

Table 3. Characteristics of patients in the case and control groups when patients were treating with thioridazine excluded from the analysis

Parameter	Case group[1]	Control group[1]	P Value
Age (Years)	33.55± 10.55	35.13± 11.10	0.70
PLC[2](meq/L)	0.40± 0.22	0.51 ±0.26	0.26
ELC[3](meq/L)	0.15± 0.14	0.28± 0.20	0.09
LR[4]	0.60±0.41	0.60±0.36	0.98
Li daily dose (mg/d)	1083.33± 234.52	1170.83± 263.05	0.35
Sr K[5] (meq/L)	4.21 ±0.45	4.20± 0.40	0.93
Sr Na[6] (meq/L)	140.78± 1.72	139.72± 2.31	0.20

[1] Values are presented as Mean± SD; [2] Plasma Lithium Concentration; [3] Erythrocyte Lithium Concentration; [4] Lithium Ratio; [5] Serum K Concentration; [6]Serum Na Concentration

Table 4. Correlation analysis between QTc and PLC, ELC, LR, Li daily dose, age, SrK when patients were treating with thioridazine excluded from analysis

Paremeter	Pearson correlation	P value
PLC[1] (meq/L)	-0.04	0.98
ELC[2] (meq/L)	-0.23	0.12
LR[3]	-0.11	0.46
Li daily dose(mg)	-0.02	0.89
Age(years)	-0.03	0.86
Sr K[4] (meq/L)	-0.04	0.79
Sr Na[5] (meq/L)	0.22	0.14

[1]Plasma Lithium Concentration; [2]Erythrocyte Lithium Concentration; [3]Lithium Ratio; [4]Serum K Concentration; [5]Serum Na Concentration

Table 5. Characteristics of patients treated with lithium alone in case and control groups

Parameter	Case group[1]	Control group[1]	P Value
Age (Years)	29.50± 11.56	33.03± 11.59	0.58
PLC[2](meq/L)	0.50± 0.17	0.44± 0.20	0.59
ELC[3](meq/L)	0.20±0.19	0.27± 0.19	0.51
LR[4]	0.44± 0.42	0.62± 0.26	0.26
Li daily dose (mg)	1237.50± 256.17	1121.05± 220.05	0.36
Sr K[5] (meq/L)	4.30± 0.29	4.21± 0.48	0.71
Sr Na[6] (meq/L)	141.50± 1.29	138.95 ±2.15	0.03

[1]Values are presented as Mean± SD; [2] Plasma Lithium Concentration; [3] Erythrocyte Lithium ; concentration; [4]Lithium Ratio; [5]Serum K Concentration; [6] Serum Na Concentration

Table 6. Correlation analysis between QTc and PLC, ELC, LR, Li daily dose, age, SrK in patients were treating with lithium alone

Paremeter	Pearson correlation	P value
PLC[1] (meq/L)	0.10	0.63
ELC[2] (meq/L)	-0.09	0.69
LR[3]	-0.05	0.82
Li daily dose(mg)	0.24	0.27
Age(years)	-0.20	0.35
Sr K[4] (meq/L)	0.08	0.73
Sr Na[5] (meq/L)	0.48	0.02

[1]Plasma Lithium Concentration; [2]Erythrocyte Lithium Concentration; [3]Lithium Ratio; [4]Serum K Concentration; [5]Serum Na Concentration

Twenty-four patients (17 males and 7 females) were treated with Li alone, of them, 20 subjects (15 males and 5 females) were in the control and 4 patients (2males and 2 females) were in the case groups. There were no significant differences in mean of ELC, PLC, LR, Li daily dose, age and serum K level between these two groups. However, serum Na levels in the case group (141.50±1.29mEq/L) was significantly higher than that of the control group (138.95± 2.15mEq/L) (P=0.03). The values of the above parameters and P values are presented in table 5. Additionally, no correlation was found between QTc and ELC, PLC, LR, age or serum K concentration of these patients. However, there was a significant positive correlation between QTc and serum Na concentration (P=0.02). The Pearson correlation and P values are shown in table 6.

DISCUSSION

Some important conditions that may cause QT prolongation include congenital long QT syndromes, heart failure, bradycardia, electrolyte imbalance, hepatic and renal impairment (6). Patients with these disorders were excluded from this study. Additionally, old age may be a cause of QT prolongation (6). In this study, there was no difference in the mean age of subjects in the case and control groups and no correlation was found between age and QTc of the subjects. Other reported determinants of QT prolongation include QTc prolonging drugs and gender (female) (6). It has been reported that thioridazine may increase risk of QTc prolongation 5.4 times more than other antipsychotic drugs (11). The present study showed that patients who were treated with thioridazine plus Li were six times more at risk for QTc prolongation than patients who were treated with Li alone.

Although some case reports and series of studies have noted haloperidol-induced QT prolongation even in therapeutic dosages by oral or intravenous routes (12, 13, 23-25), this study showed no increase in the risk of QT prolongation in patients using haloperidol concomitantly with Li. This finding was concordant with the results of some other investigations (14).

In one study, 76 subjects on similar daily dose of Li were divided to two groups based on their serum Li concentrations: those with Li plasma levels within the therapeutic range (0.6-1.2 meq/L) and patients with over-range Li levels defined as serum Li level of more than 1.2 meq/L. Results showed that QTc interval >440 ms was more commonly observed in patients with Li over range (15). In another study, it has been shown that Li induced repolarization variations are dose-related (16). In a review article, it has been concluded that cardiovascular adverse effects of psychotropic medications even in therapeutic doses are a valid concern for cardiologists (17). The findings of this study showed no relationship between QTc interval and PLC or daily Li dosage.

Some studies have shown that in comparison with PLC, ELC had better correlations with some of the side effects of Li including Li-induced renal concentrating impairment, dyskinesia and dystonia (7, 8). However, no relationship between ELC and QTc prolongation was noted in this study.

This study revealed no significant correlation between serum K concentration and QTc interval which is inconsistent with the findings of another investigation in which significant negative correlation between these two parameters are reported (14).

Similar to findings of the other study (14), this study showed no significant correlation between PLC and serum K level. Additionally, relationship between ELC and serum K concentration was not significant. In contrast to the findings of the above investigation (14), gender was not found to be affecting QTc prolongation significantly in this study.

There are several studies about the correlation between LR and Li-induced side effects, however, the results of these studies are inconsistent (7, 8, 18-22). In other recent investigations by the authors of this study, no correlations were found between LR and Li-induced renal concentrating defect, dyskinesia and/or hypothyroidism (7,8,18). Likewise, this study did not note any correlation between LR and QTc prolongation. It is concluded that

plasma or erythrocyte lithium levels are not able to predict who is prone to QTc prolongation and its consequences. Therefore, periodical ECG monitoring in patients on lithium is still suggested to detect possible QTc prolongation.

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REFERENCES

1. Ruschena D, Mullen PE, Burgess P, Cordner SM, Barry-Walsh J, Drummer OH, Palmer S, Browne C, Wallace X. Sudden death in psychiatric patients. Br J Psychiatry 1998; 172: 331-6.
2. Politi P, Piccinelli M, Klersy C, Madini S, Sagangi LG, Fratti C, Barale F. Mortality in Psychiatric patients 5 to 21 years after hospital admission in Italy. Psychol Med 2002; 32: 227-37.
3. Hannerz H, Borga P. Mortality among persons with a history as psychiatric inpatients with functional psychosis. Soc Psychiatry and Psychiatr Epidemiol 2000; 35: 380-7.
4. McEvoy GK. AHFS Drug Information. Bethesda: American Society of Health-System Pharmacist; 2002. p. 2437.
5. Committee for Proprietary Medicinal Products. Points to consider the assessment of the potential for QT interval prolongation by non cardiovascular medicine products. December 17, 1997. Available at: http://www.emea.eu.int/pdfs/human/swp/098696en.pdf . Accessed August 1 2005.
6. Haddad PM, Anderson IM. Antipsychotic related QTc prolongation, torsade de pointes and sudden death. Drugs 2002; 62: 1649-71.
7. Dashti-Khavidaki S, Ahmadi-Abhari SA, Ghaeli P, Farsam H, Dehpour AR, Mahdavi-Mazdeh M, Hatmi ZN, Fahimi F. Relationship between erythrocyte lithium concentration and renal concentrating capacity. J Clin Pharm Ther 2003; 28: 451-456.
8. Ahmadi-Abhari SA, Farhoodian A, Noroozian M, Ghaeli P, Dashti-Khavidaki S, Sadeghi M, Dehpou AR, Fahimi F. Lithium erythrocyte concentrations and neurological adverse effects in bipolar disorder. Journal of Pharmacy Practice and Research 2005; 35: 103-105.
9. Summerton AM, Harvey NS, Forrest A. New direct method of measuring red cell lithium. J Clin Pathol 1989; 42: 435-437.
10. .Chow MS, White CM. Cardiac Arrhythmia. In: Koda-Kimble MA, ed. Applied Therapeutics; The Clinical Use of Drugs. Baltimore: Lippincott Williams & Wilkins; 2001. P. 18-3.
11. Reilly JG, Ayes SA, Ferrier IN, Jones SJ, Thomas SH. QTc interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 335: 1048-52.
12. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QT interval. Expert Opin Pharmacother 2002; 3:470.
13. Roe CM, Odell KW, Henderson RR. Concomitant use of antipsychotics and drugs that may prolong the QT interval. J Clin Psychopharmacol 2003; 23: 197-98.
14. Mamiya K, Sadanaga T, Sekita A, Nabeyama Y, Yao H, Yukawa E. Lithium concentration correlates with QTc in patients with psychosis. J Electrocardiol 2005; 38: 148-151.
15. Hsu CH, Liu PY, Chen JH, Yeh TL, Tsai HY, Lin LJ. Electrocardiographic abnormalities as predictors for over-range lithium levels. Cardiology 2005; 103: 101-106.
16. Albrecht J, Muller- Oerlinghausen B. ECG changes under acute and chronic lithium application. Pharmakopsychiatr Neuropsychopharmakol 1977; 10: 325-33.
17. Burggraf GW. Are psychotropic drugs at therapeutic levels a concern for cardiologists? Can J Cardiol 1997; 13(1): 75-80.
18. Ahmadi-Abhari SA, Ghaeli P, Fahimi F, Esfahanian F, Farsam H, Dehpour AR, Jahanzad I, Hatmi ZN, Dashti S. Risk factors of thyroid abnormalities in bipolar patients receiving lithium: a case control study. BMC Psychiatry [serial online]. 2003; 3:4. Available at: http://www.biomedcentral.com/1471-244x/3/4. Accessed June 1 2003.
19. De Maio D, Buffa G, Riva M, Laviani M, Levi-Minzi A. Lithium ratio, phospholipids and the incidence of side effects. Progress in Neuropsychopharmacol Biol Psychiatry 1994; 18: 285-293.
20. Johnston BB, Dick EG, Naylor GJ, Dick AT. Lithium side effects in a routine lithium clinic. Br J Psychiatry1979; 134: 482-7.
21. Dehpour AR, Emamian ES, Ahmadi-Abhari A, Azizabadi-Farahani M. The lithium ratio and the incidence of side effects. Prog Neuropsychopharmacol Biol Psychiatry 1998; 22: 959-70.
22. Kamp JS, Oey Mirjam S, Leijnseybema HS, Most Erick VD, Van Dort-Stam Y. The lithium index in a one-year follow-up. Prog Neuropsychopharmacol Biol Psychiatry 1995; 19: 47-57.
23. Fayer SA. Torsade de pointes ventricular tachyarrhythmia associated with haloperidol [letter]. J Clin Psychopharmacol 1986; 6: 375-6.
24. Kirwisky M, Perry GY, Tarchiztky D, Kishon Y. Haloperidol-induced torsade de pointes. Chest 1990; 98: 482-4.
25. Hunt N, Stern TA. The association between intravenous haloperidol and torsade de pointes: tree cases and a literature review. Psychosomatics 1995; 36: 541-9.