Received: 26.4.2006 **Accepted: 19.8.2006**

Original Article

Lithium ratio in bipolar patients in Isfahan, Iran

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Abstract

BACKGROUND: Lithium is transferred into the intracellular space mainly via sodium-lithium counter transport pathway. This pathway is under genetic control and acts variably in different ethnic groups. With respect to possible genetic differences in our target population compared to other populations, this study was designed to obtain knowledge on mean lithium ratio (LR) in this population so as to provide a benchmark for adjusting appropriate dosage of prescribed oral lithium and plasma concentration of lithium in clinical practice.

METHODS: In this study, 47 (26 male and 21 female) patients with bipolar disorders treated by lithium alone or in combination with other drugs at least for 2 weeks were selected by simple random sampling. Venous blood samples of selected patients were obtained and plasma and RBC lithium concentrations were measured. Finally, LR was determined using the atomic absorption method.

RESULTS: Mean value of LR in the entire target population and in the group treated with lithium alone was 44.4 ± 23.22% and 58.52 ± 14%, respectively. In patients concomitantly treated with lithium and neuroleptic drugs, LR was significantly lower than that in all patients. LR in females was higher than that in males. LR in the group treated with lithium alone was significantly higher than figures reported in Europeans and Americans patients.

CONCLUSIONS: These findings suggest that bipolar patients in this geographical zone of Iran should probably be treated with smaller doses of lithium to achieve optimal intracellular therapeutic levels of lithium, compared to levels regarded as therapeutic for Europeans and Americans.

KEY WORDS: Iranian race, lithium ratio, intracellular lithium level, plasma lithium level.

JRMS 2006; 11(4): 257-262

Lithium is considered an efficient medication in prevention and treatment of some psychiatric conditions, especially bipolar disorders [1,2]. Its remedial effect is mediated via some intracellular biochemical reactions in brain tissue. There should be enough lithium in the intracellular space to achieve therapeutic effects. Excessive accumulation of lithium in the intracellular space results in toxicity, which is suggestive of the importance of lithium concentration in the intracellular space [3-6]. Intracellular concentration of lithium is influenced by its plasma concentration, as well as cellular membrane permeability to lithium [7, 8].

Numerous studies have been conducted on cellular permeability to lithium and the factors which affect it. These studies have been conducted on red blood cells (RBC) due to their availability and similarity of their functions to those of nerve cells [6]. Based on these studies, however, lithium is mainly transferred into the intracellular space with an active mechanism through sodium–lithium counter transport pathway. But, this can be affected by other factors especially concomitant use of neuroleptic drugs [4-6]. In humans, the function of this pathway depends on genetic characteristics and varies in different races [3,9-13]. Lithium ratio

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index which indicates the rate of cell membrane permeability to lithium, is determined by the ratio of RBCs lithium to plasma lithium concentration. An average of about 50% is acceptable for this index based on various pharmacokinetic and pharmacodynamic studies on lithium in European and American patients [14].

Given the possible genetic differences between Persian population and populations previously studied, this study was performed to measure LR in this population and compare it with European and American patients and also to investigate the effect of some demographic variables, as well as those of the disease and treatment process on LR in these patients, so as to provide a benchmark for adjusting the dosage of prescribed oral lithium and achieving optimal plasma lithium concentration in clinical practice.

Methods

This was a descriptive analytical cross-sectional study. The population studied comprised all bipolar outpatients and inpatients presenting to psychiatric referral centers of Isfahan (Nour, Alzahra and Farabi Hospitals), which are referral centers for many central Iranian cities. The subjects were selected by the researcher using the convenience sampling method upon visits to the above centers at different times. All of the selected patients were physically healthy based on physical examination and laboratory assessment (if needed), and had no history of hypertension, CVA, thyroid diseases, cardiac and renal diseases and hemoglobinopathies.

Only samples who had received lithium alone or in combination with other drugs for at least two weeks were included in the study. After being briefed on the goal of study and giving written consent, the subjects underwent an interview based on DSM-IV-TR to be evaluated for bipolar disorders. Later, they underwent a structured clinical interview for DSM (SCID) so that their diagnosis would be confirmed and their disease phase determined. Subjects with any obscurity in their diagnosis of bipolar disorder, those not following a regular lithium regimen and subjects not meeting general study criteria were excluded from the study.

Blood samples of selected subjects were collected as follows:

Blood samples were drawn 12 hours after the last dose of Li^+ by the researcher. The samples were collected upon regular hospital visits in Vacutainer tubes containing edetic acid anticoagulant. A method for direct measurement of erythrocyte Li^+ concentration was used. The samples were centrifuged at 1600 × g for 10 minutes and the plasma was removed by aspiration. A 1:20 dilution in distilled and deionized water was made of 99 µl of plasma. 200µl of packed erythrocytes was dispersed into 1 ml of 150 Mm choline chloride (Sigma Chemical Company, USA.), which was layered on 0.2 ml of dibutyl phthalate in a 1.5 ml microfuge tube. The samples were immediately centrifuged at 8800 × g for 2 minutes in a microcentrifuge (Hettich, Germany). Dibutyl phthalate has a density between that of water and erythrocytes. The erythrocytes were therefore precipitated to the bottom of the tube, with the passage through the dibutyl phthalate removing the adherent plasma. A 1:20 dilution of packed cells was made and mixed thoroughly to ensure complete hemolysis. Both plasma and erythrocyte lithium concentrations were measured using a Perkin-Elmer 2380 Atomic Absorption Spectrophotometer (USA). Readings were made in triplicate at a wavelength of 670.8 nm. Peak height measurements were compared with values for standards of known concentrations made up in similarly diluted plasma and erythrocyte.

Forty-seven qualifying samples were included in the eight-month study. As some of the patients were on antipsychotic medications in addition to lithium carbonate, the patients were divided into four groups as follows:

Group 1: 13 patients taking a phenothiazine antipsychotic drug (perphenazine, chlorpromazine, thioridazine or trifluoperazine) in addition to lithium carbonate at therapeutic dosage.

Group 2: 8 patients taking lithium carbonate with olanzapine 5- 10 mg/day.
Group 3: 14 patients taking lithium carbonate alone.
Group 4: 12 patients taking other antipsychotic drugs (except phenothiazines and olanzapine) along with lithium carbonate.
The collected data were analyzed with SPSS using t-test to compare LR in the two sexes. ANOVA was used to define the association between various mood phases with LR., One-way ANOVA was used to compare mean LR in the four groups and Duncan test to compare groups two by two. Pearson correlation test was also used to define the association between age and LR. One sample t-test was used to compare mean of LR in the studied population with mean of LR reported in previous studies.

Results

A total of 47 patients (26 males and 21 females) with a mean age of 29.2 ± 10.57 years were studied. There were 20 patients in depression and 27 in mania phases. Mean lithium dosage taken by the studied patients was 960.6 ± 201 mg/day and mean LR appeared to be 44.39%. Of notable interest was the considerably low level of LR in men compared to women (table 1) The most important finding in correlation analysis results for the different variables (table 2) was the inverse significant correlation between age and LR. There was no significant correlation between disease phase and LR (P = 0.39). The findings showed that LR was significantly different in the four groups (P = 0.008) (table 3). The highest LR was seen in those taking lithium carbonate alone and the lowest in those taking phenothiazines and lithium.

Co-variance analysis showed that the difference between four groups is not due to sex or age. The influence of sex on LR already demonstrated by our findings was reinvestigated in the four groups. Independent t-test revealed that in each of the four groups LR is significantly higher in women than in men.

Table 1. Received dosage, plasma and RBC levels of lithium and LR, based on sex and age.

Sex	N	Age			Lithium Dose mg/day	Plasma Lithium mEq/L	R.B.C Lithium mEq/L	LR
		Mean	Min	Max	Mean	Mean	Mean	Mean
Male	26	30.9 ± 10.31	600	1500	980.7 ± 232	0.68 ± 0.30	0.25 ± 0.19	36.18 ± 18.22
Female	21	27.2 ± 11.21	600	1200	935.7 ± 156	0.59 ± 0.26	0.31 ± 0.22	54.57 ± 25.08
Total	47	29.2 ± 10.57	600	1500	960.6 ± 201	0.64 ± 0.28	0.28 ± 0.21	44.40 ± 23.22

Table 2. Data correlations related to studied variables

	Pearson Correlation (r) and P-value				
Variables	LR	Lithium Dose	Age	Duration of Lithium intake	Plasma Lithium
Lithium Dose	r = -0.031 P>0.05				
Age	r = -0.278 P = 0.029	r = -0.069 P>0.05			
Duration	r = 0.017 P>0.05	r = 0.022 P>0.05	r = 0.258 P = 0.040		
Plasma Lithium	r = -0.138 P>0.05	r = 0.316 P = 0.015	r = 0.070 P>0.05	r = -0.007 P>0.05	
RBC Lithium	r = 0.676 P = 0	r = 0.247 P = 0.047	r = -0.182 P>0.05	r = -0.072 P>0.05	r = 0.534 P = 0

P>0.05, r = 0: there was no significant correlation between two variables.
P<0.05, r<o: there was an inverse significant correlation between two variables.
P<0.05, r>o: there was a direct significant correlation between two variables.

Table 3. The correlation between LR and the type of received medication combined with lithium in patients of the study group.

Group	N	Mean Lithium Dose (mg/day)	Mean Plasma Lithium Concentration mEq/L	Mean RBC Lithium Concentration mEq/L	Mean LR mEq/L
I	13	957.70 ± 168	0.709 ± 0.299	0.184 ± 0.071	27.90 ± 10
II	8	937.50 ± 175	0.680 ± 0.257	0.227 ± 0.134	35.35 ± 21
III	14	942.86 ± 260	0.481 ± 0.235	0.273 ± 0.158	58.52 ± 14
IV	12	975.00 ± 226	0.729 ± 0.285	0.412 ± 0.326	51.85 ± 22
Total	47	960.60 ± 201	0.640 ± 0.280	0.280 ± 0.210	44.40 ± 23

Group I: lithium carbonate + phenothiazines
Group II: lithium carbonate + olanzapine
Group III: lithium carbonate
Group IV: lithium carbonate + other antipsychotic drugs

Pearson correlation test revealed that LR had no association with dosage of lithium and duration of intake. Mean lithium LR in the target population first appeared to have an inverse correlation with age, but after dividing the population into four groups, Pearson correlation test showed LR in each of the groups to be unrelated to age. Based on one sample t-test, mean LR (58.52 ± 14%) in the group treated with lithium alone was significantly higher than 50% of acceptable mean LR in previous studies [14].

Discussion

As found in previous studies, sodium-lithium counter transport pathway in cell membrane functions based on genetic characters [9,10]. Genetic differences can thereby affect the amount of lithium in erythrocytes resulting in LR changes; this has been demonstrated by various comparative studies in different racial groups [11-15]. Although initial mean LR in subjects of this study was less than 50% (44/40%) of accepted LR in previous studies [14], LR increased noticeably after confounding factors such as simultaneous intake of other medication were taken into account via assigning the subjects to four groups based on concomitant use of other drugs. Mean LR in patients taking lithium carbonate alone was significantly higher than the levels reported by African–American and Caucasian racial studies [12] and significantly higher than those reported by Ward and colleagues (i.e. 50% in patients taking lithium carbonate alone) [14]. Mendels implied that [16], patients with LR>50% were recognized as having higher LR and showed better response to treatment with lithium and were described as responders. On the other hand, patients with LR<50% showed a lower response to treatment and were known as non-responders.

Compared to the Mendels view, our studied population had higher LR and can be described as a responding population. Another finding in this study was that LR depends on sex and is seen more among women compared to men. The latter finding was independent of confounding variables; this is consistent with the results of Lyttkens study [17]. In the present study initial mean LR appeared to have an inverse correlation with age. However, after the target population was divided into four groups, the primary results were not repeated within the groups. Therefore primary results were probably due to the confounding effects of neuroleptic drugs and sex distribution in the target population. No correlation was found between age and LR, a result also reported by Von Knorring study [18].

In the present study, LR had no correlation with mood phase of the bipolar patients, but Mallinger AG [19] reported higher LR in the depression phase. In this study, LR appeared to have no association with dosage of lithium and length of intake. Some of the patients in this study received neuroleptic drugs at therapeutic doses combined with lithium carbonate; our

comparative investigation revealed that simultaneous intake of lithium and neuroleptic drugs, especially phenothiazine, decreases LR. This effect is lower with olanzapine, a finding also reported by Ghadirian study [20]. It was also seen that other neuroleptic drugs have a lower negative effect on LR compared to phenothiazine and olanzapine. It can be concluded that the LR-decreasing effect of phenothiazine and olanzapine is noticeably more than this effect by other neuroleptics. The effect of neuroleptic drugs (especially phenothiazine) on LR may be mediated through the stabilizing effect of these drugs on the cell membrane and consequently lithium transport in erythrocytes. The subjects in the present study were chosen according to strict selection criteria. Furthermore, RBC lithium concentration was measured with the direct method which is more precise than old techniques. Thus, the present study can be considered to be of high reliability [21].

Based on our findings, while much care should be taken in adjusting lithium dosage in women, LR-decreasing effects should also be heeded when administering lithium carbonate simultaneously with neuroleptics, especially phenothiazine and olanzapine. Finally, significant differences of LR in our studied population compared with previous studies suggest that an optimal therapeutic intracellular level of lithium can be achieved with lower doses of lithium in this region of Iran. This is of great importance for reducing the risk of lithium toxicity. Hence, to achieve optimal intracellular therapeutic levels of lithium in patients in Central Iran, they should probably be treated with smaller doses of lithium compared to those considered as therapeutic for European and American races.

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