The Effect of Concurrent Administration of Typical or Atypical Antipsychotic Drugs and Lithium on Lithium Ratio in Acute Manic Patients

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Objective: The lithium concentration in the plasma is assumed to give some indication as to the concentration of this ion in different organ cells especially in central nervous system. While the practical value of intracellular lithium measurement is controversial however, erythrocytes have proved to be useful for studying lithium concentration and its transport across the membrane. There are some reports suggesting that neuroleptic drugs are able to affect the erythrocyte lithium concentration (ELCs), although these studies have yielded inconsistent results.
Method: In the present study the effect of risperidone and olanzapine as atypical antipsychotic and haloperidol as standard typical antipsychotic on lithium ratio in 46 acute manic patients was studied. ELCs were measured using atomic absorption spectrophotometer. Clinical response was evaluated by using Young mania rating scale (YMRS).
Results: No significant difference was found between LRs and dose or type of antipsychotics. Also there were no significant differences between LRs and clinical response or remission.
Conclusion: The concurrent use of an atypical antipsychotics and lithium may not significantly alter the lithium transport in the erythrocyte and presumably in the nerve cells. A more comprehensive study is warranted to confirm the results of this study.

Key Words:
Antipsychotic agents, Atomic Spectrophotometry, Bipolar disorder, Erythrocyte, lithium

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Lithium is one of the most widely used mood-stabilizing agents for the treatment of bipolar disorder. Lithium ratio is defined as the erythrocyte lithium concentration divided by plasma lithium concentration. Intra-neuronal lithium concentration may be better correlated to erythrocyte concentration than to plasma concentration (1-3). There are some reports suggesting that neuroleptic drugs are able to affect the erythrocyte lithium concentration, although these studies have yielded inconsistent results (4-6). In our previous study we considered the effect of concurrent administration of psychotropic drugs, including different types of typical neuroleptics on lithium ratio in bipolar patients (4). In the present study the effect of risperidone and olanzapine as atypical antipsychotics and haloperidol as standard typical antipsychotic on lithium ratio was studied.

Materials and Method

This is a prospective cohort study in which all of the patients had manic episode and were receiving lithium in nearly equal doses.
In this study, the first group were receiving lithium in combination with typical antipsychotic (Haloperidol) and second group were those receiving lithium in combination with an atypical antipsychotic (Risperidone or Olanzapine). This is a Survey onbipolar patients and no other intervention was arried out.

Participants
Of a total of 126 manic patients who were admitted to Roozbeh Hospital of Tehran University of Medical Sciences, 80 patients were divided into two groups: patients treated with 1. Lithium combined with haloperidol (n=40), 2. Lithium combined with one atypical antipsychotic (n=40). Mean dosage of lithium was 1076±208 mg and mean equivalent dosage of antipsychotic was 8.6±4.5 mg. There was no significant difference between two groups in lithium and antipsychotic dosage.
All patients were diagnosed according to DSM-IV diagnostic criteria for manic episode. The exclusion criteria were 1- schizoaffective disorder, 2-mixed episode; 3- substance related disorders; 4- rapid cycling BMD, 5-Mood disorder due to general medical condition; 6- receiving a variety of other medications.

The remaining 34 patients were excluded from this study because they were receiving a variety of other medications in combination with lithium or had one of the above exclusion criteria at the time of discharge from hospital or because of hemolysing the blood samples before they were centrifuged.
At the beginning of study Young mania rating scale (YMRS) was used to rate the severity of the manic symptoms and at the end of the study, patients were again assessed by YMRS.
Informed consent was signed by the selected patients/family.

Collection of blood samples and determination of lithium concentrations

Blood samples were drawn 12 h after the last ingested dose of lithium. The samples were collected in tubes containing edetic acid anti coagulant. The direct method of measuring the ELC was used (7). The samples were centrifuged at 1600 g for 10 min and the plasma was removed by aspiration. A 1:50 dilution in distilled and deionized water was made of 99 ml of plasma. Furthermore, 200 ml of packed erythrocytes were dispersed into 5 ml of 150 mM choline chloride (Sigma Chemical Company, USA), which was layered on 1 ml of dibutyl phthalate. The samples were immediately centrifuged at 8800 g for 2 min in a micro centrifuge (Eppendorf, Germany). Dibutyl phthalate has a density between that of water and erythrocytes. The erythrocytes were therefore sedimented to the bottom of the tube, passage through the dibutyl phthalate removing the adherent plasma. A 1:50 dilution of packed cells was made and mixed thoroughly to ensure complete hemolysis. Both plasma and erythrocyte lithium concentrations were measured using a Shimadzu AA-670 Atomic Absorption Spectrophotometer (Shimadzu, Japan). 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 erythrocytes.

Statistical analysis

The data were analyzed with statistical package for the social sciences (version 11.5). Data were analyzed using unpaired student t-test and Fisher's exact test.
A logistic regression analysis was performed to find out any relationship between LRs and response or remission rate. A 95% confidence limit was used as significance level.

Result

Thirty six patients completed this randomized study Of the 80 patients who met the inclusion criteria, 34 patients were excluded. There were no significant differences between dropouts and completers in demographic and clinical variables.
Of 46 patients who completed the study, there were 30 males and 16 females with mean age of 31.4 years.

The mean Plasma lithium concentration (PLCs) was 0.74 (SD=0.26), mean erythrocyte lithium concentration (ELCs) was 0.27 (SD=0.13) and mean lithium ratio (LRs) was 0.39 (SD=0.24).
There was no significant difference between two groups in PLCs, ELCs, LRs, lithium dosage and antipsychotic dosage. Also there was no significant correlation between the LRs and antipsychotic dosage or lithium dosage.
We defined clinical response as 50% or greater reduction in YMRS score at forth week compared with baseline and remission rate was defined as YMRS score≤ 12 at the end of the study (Li H etal). According to this definition, remission rate was 82.6% (n= 38) and response rate was 91.3 %(n=42). There was no significant difference between two groups in remission rate and no significant correlation between LRs and remission rate. Also remission rate showed no significant correlation with age or sex or lithium dosage or antipsychotic dosage.

Discussion

The results of the present study revealed that patients treated with a combination of lithium and Haloperidol or atypical antipsychotics showed no significant differences in LRs and ELCs .
Previous investigators have published similar results to ours. For example, the in vitro study (8) and the in vivo studies (9) showed no significant difference when lithium was combined with haloperidol. However, the present findings are different from some other studies (4, 5, 10) . One reason that might provide an explanation for these discrepant results is the difference in methodology. It has been shown that the indirect method gives much more variable and less accurate results than the direct method (7, 11). In the present study we have used new direct method of measuring ELC that have proven its accuracy and precision (7). Another reason for these inconsistent results may be related to patient selection. It was observed that in depressed patients, the lithium ratio was higher than in healthy subjects (12) and also higher than in patients with schizophrenia and schizoaffective illness (13). Among affective patients, the ratio was higher in bipolar than in unipolar patients (12, 14). In the present study we selected only manic patients and excluded other psychiatric disorders that may resemble a manic episode, such as schizoaffective or substance abuse related disorders and also some special types of mood disorders such as mixed episodes or rapid cycling BMD. However, other studies which have already been cited included patients with different types of disorders (8, 9, 14). Moreover, we only selected inpatients because some studies reported different LRs during the episode and during maintenance lithium therapy (3, 15-17), and this factor may have had a confounding role in some previous studies .
Moreover, several groups of investigators have reported that patients who show a good response to lithium have higher ELCs and higher LRs than those

who do not respond well (18-21). However, our findings showed no significant correlation between LRs and response rate or remission. Although, our sample was small for evaluating this correlation, but this finding is consistent with some other studies. (22-24).

In conclusion, the concurrent use of an atypical antipsychotics and lithium may not significantly alter the lithium transport in the erythrocyte and presumably in the nerve cells, since it has been reported that there is a significant positive correlation between lithium transport in erythrocyte and that in brain (2). Further research is needed in order to thoroughly evaluate the effects of psychotropic drugs on erythrocyte lithium levels in the treatment of BMD.

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