ORIGINAL ARTICLE

MOOD STABILIZING AGENT LITHIUM CARBONATE DEPLETES REDUCED GLUTATHIONE IN HUMAN ERYTHROCYTES DURING LITHIUM TOXICITY

Hashmat Ullah, Muhammad Farid Khan
Department of pharmaceutical chemistry, Faculty of Pharmacy Gomal Univeristy, D.I.Khan, Pakistan

ABSTRACT

Background: Lithium carbonate is commonly used as mood stabilizing agent but it is so toxic that even its therapeutic dose can cause toxicity. Present work was designed with the aim that whether it has any effect on reduced form of glutathione in human erythrocytes.

Material & Methods: It was an experimental study conducted in PhD research laboratory, Faculty of Pharmacy, Gomal University, D.I.Khan during the month of January 2013. Six human volunteers of age group 21-24 years were selected for obtaining fresh blood. Exactly 15ml blood was collected from each volunteer. Erythrocyte's GSH was treated with different concentrations of lithium carbonate. One-way ANNOVA was applied to test the statistical significance.

Results: The decrease in erythrocytes GSH was 31.68%, 34.16%, 37.02%, 38.90%, 40.91% and 43.01% respectively from lowest to highest used concentration of lithium carbonate. A significant decrease in GSH level was observed as lowest one concentration of lithium carbonate has significantly ($p<0.005$) decreased GSH which was up to 31.68% and this decrease was further noted with the passage of time indicating that during lithium toxicity depletion of erythrocytes GSH is dose and time dependent hence early measures for lithium detoxification guaranteed patient's safety.

Conclusion: Of course lithium is extensively used as mood stabilizer as well as for the treatment of manic depressive psychosis but experts should keep in mind that it is the cause of depletion of GSH in erythrocytes so precautions must be taken during lithium therapy.

KEY WORDS: Erythrocytes; Lithium Carbonate; Therapeutic; Mood stabilizing agent.

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INTRODUCTION

Lithium carbonate is widely used as mood stabilizer throughout the word while its use as a therapeutic agent for the treatment of manic depressive psychosis is also very common.[1,2] Lithium is highly effective against acute mania.[3-6] The present data is very stronger regarding effectiveness of lithium in the maintainance phase.[7-12] Lithium therapy drawbacks include its poor tolerability, especially at higher doses, and risk of "rebound mania" on withdrawal.[13] General unwanted effects of lithium are tremor, polydipsia, polyuria, and in the long-term, hypothyroidism. But, in spite of all these side effects, lithium is still gold standard of treatment. In addition to this, it also has an antisuicidal effect.[14,15]

Corresponding Author:
Hashmat Ullah
Faculty of Pharmacy
Gomal University
D. I. Khan, Pakistan
E-mail:drhashmat28@gmail.com

Lithium overdose is always a cause of lithium toxicity because lithium has narrow therapeutic index.[16] Lithium toxicities in kidneys, thyroid function , intestine, liver, brain and in many other vital organs and systems have been investigated.[17,18] In brain along with other changes L^{+1} alerts activities of enzymes glutathione peroxides and superoxides dismutase[19] while in kidneys malondialdehyde levels were found increased following lithium treatment.[20] When lithium is used in its carbonate form, it is found that carbonate causes selective increase of L^{+1} and Na^{+1} permeability [21,22] which is due to ability of carbonate to form ion pairs with lithium and sodium. In vitro studies it has been shown that lithium is extruded against an electrochemical gradient by a counter transport mechanism which depends on the presence of an opposite directed gradient for so-

dium ion.[23,24] The lithium gradient across the human red blood cells can only be sustained if the passive lithium permeability remains low. A large capacity for lithium sodium counter transport has been found in bovine[25] in contrast to much smaller capacity of human red blood cells.[26]

Present work was designed with the aim that whether it has any effect on reduced form of glutathione in human erythrocytes.

MATERIAL AND METHODS

Fifteen ml of whole blood was taken and processed for isolation of different components of blood by centrifugation process. After the separation of different blood components, one set of 6 test tubes was prepared of cytosolic fraction obtained from erythrocytes. In the set of 6 test tubes prepared for cytosolic fraction, 2000μl of cytoslic fraction was added to which 2000μl of different concentration of LiI was mixed and incubated for 10 minutes. These are reaction mixtures of cytosolic fraction plus different concentrations of Li^{+I}. Now a set of another 6 test tubes was prepared, each test tube containing 2300μl of phosphate buffer saline pH 7.6 and to each test tubes 200μl of cytosolic fraction plus different concentrations of Lithium carbonate was mixed followed by addition of 500μl of DTNB and was incubated for 5 minutes. After the incubation time, absorbance of each sample mixture was recorded at fixed wave length λmax: 412nm under UV-visible spectrophotometer. The absorbance of each sample was then converted to concentration of GSH. The chemical and instruments used in this research were Ellman's reagent, reduced form of glutathione (GSH) (Fluka), ethanol, chloroform, potassium dihydrogen phosphate (sigma), Lithium carbonate (sigma), UV-visible spectrophotometer of shimadzu model-1601, Japan, pH meter (Nov-210, Korean Nov scientific company), centrifuge model H 200 Kokuson Ensik company of Japan, disodium edetate, NaOH, NaCl (Merk), HCl (Kolchlight).

RESULTS

The results are depicted in the figures below. (Fig. 1-3)

DISCUSSION

Although lithium is very much effective in manic as well as in depressive episodes associated with bipolar disorder and is often used for long term maintenance but at the same time physicians must be aware of lithium toxicities. As a matter of fact it is the only mood stabilizer with anti-suicidal effect.[21,22] and is considered to be the best treatment in patients having strong family history of bipolar disorder.[23] A target therapeutic serum level of 0.6-0.75 mEq/L is recommended for the treatment of bipolar

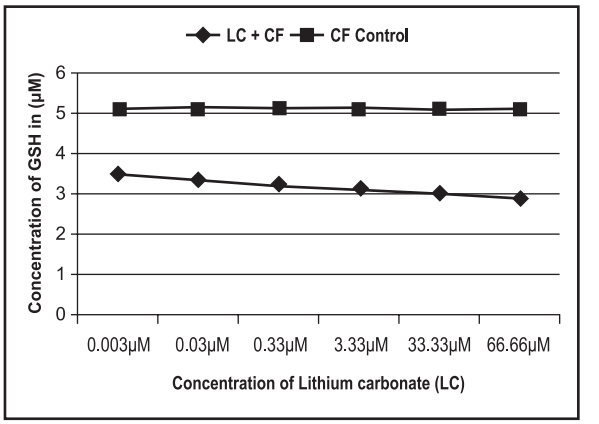

Figure 1. Effect of different concentrations of lithium carbonate (LC) on the chemical status of erythrocytes cytosolic fraction-GSH level. Results are the mean ±SE of 3 experiments of cytosolic fraction GSH.

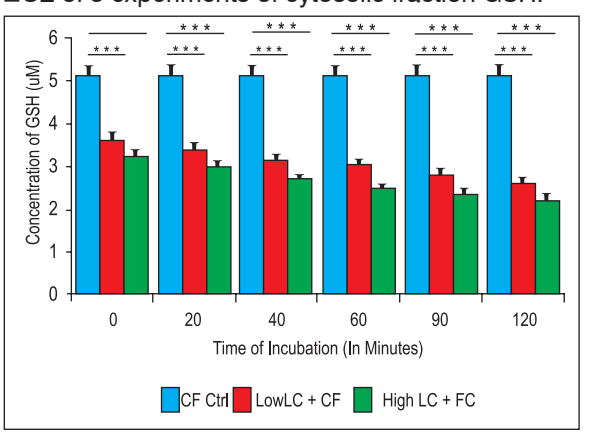

Figure 2. Effect of lowest and highest used concentration of lithium carbonate on erythrocyte cytosolic fraction GSH with time. Results are the mean ± SE of 3 experiments of cytosolic fraction GSH.

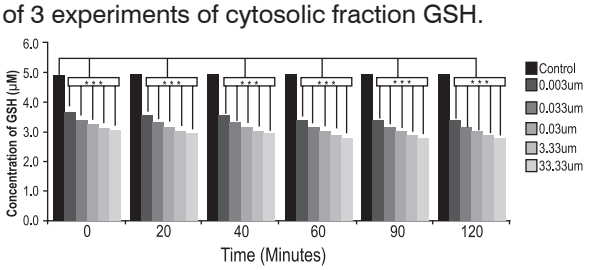

Figure 3: Result of effect of different concentration of lithium carbonate (LC) on cytosolic fraction GSH with time (i.e. 0 min ,20min ,40min ,60min ,90min ,120 min) Results are the mean ± SE of 3 experiments

depression and prophylaxis against depressive relapses.[23,24] Serum levels of 0.75-1.2 mEQ/L may be more effective for the treatment of mania. Serum levels higher than 1.2 mEq/L are associated with significant lithium toxicity. Our results show that lithium depletes reduced glutathione in erythrocytes during lithium therapy in general and in lithium toxicities in particular. Side effects frequently increase with higher serum doses but can arise at any dose. Nausea,

vomiting, diarrhea, tremor, thirst, polyuria, acne, weight gain, and a benign leukocytosis are major side effects. Lithium can cause hypothyroidism and deterioration of renal function in about 20 percent of patients.[25,26] Our results suggest that physicians should be aware that the anti-manic effects of lithium may not be achieved until 7-10 days after a therapeutic dose has been established. Meanwhile sedative medications such as antipsychotics and benzodiazepines may be required when the patient is acutely manic. Once the patient is stabilized, these additional medications must be stopped and lithium sustained as monotherapy .It was also observed that with increasing time period, there was further drop in GSH levels of erythrocytes which indicating the fact that during lithium therapy antioxidants or their precursors must be given as adjunctive therapy and during lithium toxicities along with other treatment for lithium detoxification, antioxidant must be given to the patients.

CONCLUSION

Lithium carbonate depletes reduced glutathione in erythrocytes cytosolic fraction and this depletion is dose dependent so physicians must be aware of this fact during treating different psychiatric disorders with lithium carbonate.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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