Seasonal variation in plasma levels of lithium in the Indian population: is there a need to modify the dose?

Medhi B, Prakash O, Jose V M, Pradhan B, Chakrabarty S, Pandhi P

ABSTRACT

Introduction: Lithium still remains an important choice in the therapy of manic-depressive psychosis (MDP), and though there are reports of seasonal variation in lithium levels from a few countries, such studies have not been conducted in India. Variability in the lithium level can lead to lack of efficacy or toxicity, making seasonal variation clinically relevant.

Methods: A retrospective case sheet audit was performed for 101 MDP patients for recording plasma lithium level, oral lithium dose, age and gender for one year. The overall average oral lithium dose and level were recorded; the monthly average to which it most closely matched was noted as the control month, and values of other months were compared with this control month by Friedman's test followed by Dunn's test.

Results: The mean age of patients was 38.22 (standard deviation 12.07) years, and 72 out of 101 patients were male. The mean lithium dose in November (938.61 +/- 243.40 mg/day) , which was the closest to the overall mean dose (938.24 +/- 241.78 mg/day) was taken as the control month, which when compared with other monthly values, did not show any significant difference. The June (0.54 +/- 0.23 meq/L), July (0.55 +/- 0.24 meq/L) and August (0.55 +/- 0.24 meq/L) mean plasma lithium values were significantly high when compared to the October value (0.45 +/- 0.22 meq/L) as control. High-low variability between the plasma lithium values of different months was found to be 25 percent.

Conclusion: The present study showed a significant high variability of lithium levels in different months of the year, therefore frequent plasma level monitoring and oral lithium dose adjustment to prevent situations of toxicity and lack of efficacy in MDP.

Keywords: lithium, manic-depressive psychosis, oral lithium, seasonal variation in plasma lithium, therapeutic drug level monitoring

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INTRODUCTION

Lithium still remains a very useful drug in the treatment of manic-depressive psychosis (MDP), irrespective of the recent advances in the field of psychiatry.[1-3] It is a monovalent cation which shows a high degree of interindividual variation and narrow therapeutic index.[4-9] Hence, variability in lithium levels has to be viewed with caution since it can affect the efficacy and safety in the patient. Seasonal variation in lithium levels have been reported in the literature from Italy, the Netherlands and the United States.[10-12] Because of the subtropical geographical location of India, a higher variation in lithium levels is expected though no studies have been conducted to confirm this. Hence this study was conducted to determine whether there exists any change in the plasma lithium level during different seasons of the year. If variation in the plasma lithium level is observed, then oral dose modification will be needed for management to avoid toxicity, as well as loss of efficacy in the different seasons, thereby bringing more relevance to therapeutic drug level monitoring (TDM) of lithium, which will be required at more frequent intervals. This can also provide an alternative explanation for variation in MDP symptomatology clinically observed in the different seasons.

METHODS

This retrospective case sheet audit for lithium levels was done at Psychiatry Outpatient Department, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Patients of either gender diagnosed with MDP and on regular treatment in the hospital with lithium for at least a year and had undergone TDM at least four times, were included in the study. Situations of lithium use other than MDP were excluded. Data was collected by a trained doctor in the year 2005. Plasma lithium level, lithium dose administered, age and gender were noted. Anonymity of the patient data was maintained. The drug lithium manufactured by all the companies was used in the hospital during the study period. Plasma lithium levels of 0.35–1.0 meq/L was the efficacious target maintenance level followed in our hospital, in spite of other opinions.[13-15]

Department of Pharmacology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India

Medhi B, MBBS, MD, FIMSA
Associate Professor

Prakash O, MBBS, MD
Senior Resident

Jose VM, MBBS, MD, DM
Senior Resident

Pandhi P, MBBS, MD, DM
Head

Department of Psychiatry

Pradhan B, MBBS, MD
Senior Resident

Chakrabarty S, MBBS, MD
Associate Professor

Correspondence to:
Dr Bikash Medhi
Tel: (91) 172 275 5250
Fax: (91) 172 274 4401
Email: drbikashus@yahoo.com

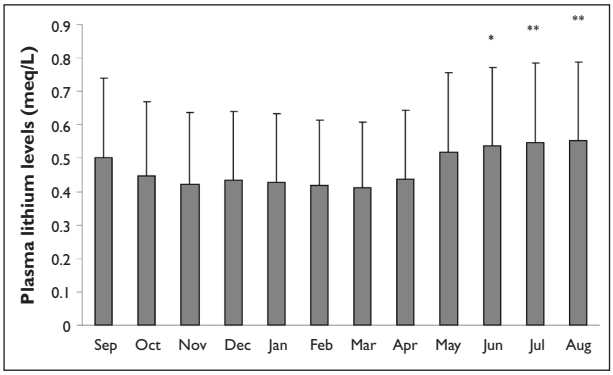

Fig. 1 Bar chart shows the comparison of the plasma lithium levels (mean ± SD) over the months with respect to October as the control month.
Analysis was done by Friedman's test followed by Dunn's test. Fr value: 115.08, $p < 0.001$.
*$p < 0.05$; **$p < 0.01$

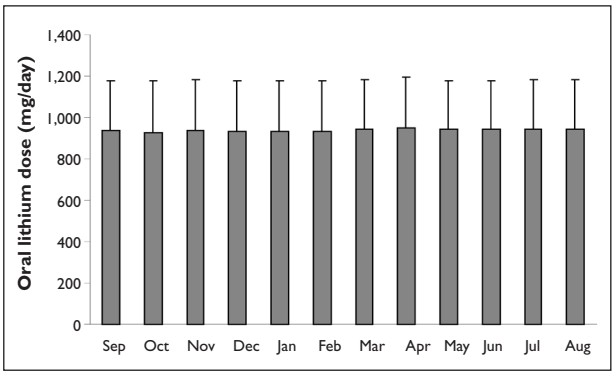

Fig. 2 Bar chart shows the comparison of the different doses of lithium (mean ± SD) taken per month compared to the control month, November.
Analysis was done by Friedman's test followed by Dunn's test. Fr value: 2.84, $p = 0.99$.

Plasma lithium was analysed using a 654 sodium/potassium/lithium analyser (Ciba Corning Diagnostic Ltd, Halstead, Essex, England). The principle is based on the potential developed by the lithium ion selective electrode with respect to the reference electrode. In an electrolyte solution, most sample salts dissociate to their ions. An electrolyte exchange reaction occurs between the relevant electrode and the ion which produces a potential between the ion selective electrode and the reference electrode. The reference electrode provides a fairly constant potential irrespective of the matrix being analysed. Nernst equation will provide the electrode potential developed. Lithium ion selective electrode consists of a neutral carrier-based lithium sensor immobilised in polyvinyl chloride. Electrical connection is by silver or silver chloride wire. The reference electrode consists of a shell filled with saturated potassium chloride separated from the sample by a membrane. Electrical connection is by a silver or silver chloride wire coated with nafion, an ion permeable polymer. This method is resistant to climate changes.

To study the variability of lithium level in patients with a confidence interval of 95% and variability of 10%, the most conservative sample size required was 97 patients. Hence, we decided to include data from 101 patients for the study. A p-value < 0.05 was considered as significant. The average dose of lithium used every month was determined; the last value was carried forward for any missing dose. The average plasma lithium level was determined; for missing values, the next first value was carried backwards. The mean of all plasma lithium levels and oral lithium dose were respectively determined. The month with the closest value to the total mean value was then determined, irrespective of the standard deviation (SD), and was taken to be the reference value. Other months' values were compared with this reference value using Friedman's test followed by Dunn's test, by using the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). If more than two lithium levels were done in the same month, the mean of these values were considered as the value of that month. Ten randomly-selected patient charts were cross-checked by another investigator for confirming the accuracy of the initial data collection.

RESULTS

Data from 101 patients was collected. 72 (71.3%) were males and the mean (SD) age was 38.22 (± 12.07) years. The overall average dose of lithium taken by the patients was 938.24 (± 241.78) mg/day. Since the November mean lithium dose taken (938.61 ± 243.40 mg/day) was closest to the mean dose, this value was taken as the control value with which other values were compared. The oral dose of lithium did not show any significant difference from the control value. The overall mean plasma lithium value was 0.47 ± 0.23 meq/L. Since the October mean plasma lithium value (0.45 ± 0.22 meq/L) was the closest to the mean, this value was taken as the control and all other values were compared with it. The plasma lithium values of June, July and August were significantly high, compared to the control value. Maximum difference observed for lithium levels between the different months was 25% (Figs. 1 & 2).

DISCUSSION

There was convincing evidence of higher plasma lithium levels observed in June, July and August compared to October (control). The oral lithium dose did not show any significant difference over the months. Hence, it

could be concluded that plasma lithium levels showed significant seasonal variation among MDP patients who were put on long-term prophylaxis with lithium. However, the mean plasma lithium values in all the months were within the normal range throughout the study period. There was a 25% variation observed in the lithium levels during the different seasons in this study. Studies done in Italy, the Netherlands and the United States have shown higher lithium levels in summer.[10-12] Patients with an early onset of MDP had showed greater variation in the lithium levels.[10] Variations observed in Italy was 10% and in the Netherlands 5%.[10,11] Lithium, because of its narrow therapeutic index and marked interindividual variation, requires TDM in those patients who are on prophylaxis.[4-9] Considerable variation in lithium levels during the different seasons can lead to lithium toxicity in summer and lack of efficacy in winter. Hence, this observation further strengthens the need of more frequent lithium monitoring. Perspiration leading to loss of sodium and water from the skin, leading to a compensatory increased reabsorption of monovalent cations like lithium from the nephrons, is suggested to cause this increased level.[10] Increased perspiration due to a hotter climate in India (compared to Italy and the Netherlands) seems to explain the higher variability in India.

Seasonal variation in the incidence of psychiatric illnesses, like bipolar disorder, suicide, mania, depression and schizophrenia, have been observed and its potential relation to temperature variation has been suggested.[16-19] Cortisol levels after dexamethasone suppression test in depressed males, L-tryptophan availability in plasma, monoamine metabolites and neuropeptides in cerebrospinal fluid (CSF), 5-hydroxyl indole acetic acid and homovanillic acid levels in CSF, mood response following L-tryptophan administration and thyroid hormone levels, have been studied for a potential explanation of the seasonal pattern of these illnesses.[20-24] It is observed that lithium is more retained in the body during the manic phase, following improvement of which there is increased urinary excretion.[25] Lithium distribution pattern in manic and normal individuals have showed differences.[25] There are conflicting observations regarding the response of psychiatric illnesses to lithium in different seasons.[11,26] These observations have led to the dilemma that lithium variation is secondary to the disease pathophysiology or disease variation is secondary to lithium level variation. However, there is no alternative to the maintenance of plasma lithium with a clear-cut limit for optimum benefit and to avoid toxicity.

Only confirmed MDP patients who were on continuous follow-up for a minimum period of a year, including only severely-ill patients, were included in the study. Concomitant drugs were not monitored, but it was expected not to interact with the lithium levels since these precautions are usually taken when drugs are prescribed in a tertiary care facility. Accuracy of the drug level estimation, which depends on the timing of the blood sample with respect to lithium intake, sample transportation, storage and estimation procedures, were expected to be standardised since this is a routine procedure in the hospital.[9] Being a retrospective study, the inability to cross-check the accuracy of the plasma lithium levels was unavoidable. Total number of actual plasma lithium levels estimated in the different months varied throughout the year, thereby necessitating a carry-over technique to substitute for the missing values. Most of the above-mentioned problems were unavoidable in any retrospective study. However, the increased variability observed, compared to the earlier studies, strongly indicates that hot climates with high humidity are the cause of the variation. Similar studies in different latitudes and longitudes of the world should be conducted to verify this finding.

It could be concluded that in a subtropical country like India, there are seasonal variations observed in plasma lithium levels of up to 25%, with no significant change in the oral lithium dosage. This implies that frequent drug level monitoring and oral dose adjustment of lithium are required to avoid significant variation in plasma lithium levels which can otherwise lead to toxicity or lack of efficacy, especially since lithium is a drug that follows a narrow therapeutic index.

REFERENCES

1. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005; 162:1805-19.
2. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004; 161:217-22.
3. Poolsup N, Li Wan Po A, De Oliveira IR. Systematic overview of lithium treatment in acute mania. J Clin Pharm Ther 2000; 25:139-56.
4. Sachs GS, Renshaw PF, Lafer B, et al. Variability of brain lithium levels during maintenance treatment: a magnetic resonance spectroscopy study. Biol Psychiatry 1995; 38:422-8.
5. Hopkins HS, Gelenberg AJ. Serum lithium levels and the outcome of maintenance therapy of bipolar disorder. Bipolar Disord 2000; 2:174-9.
6. Moody J P. Biologic variation of serum and salivary lithium. Ther Drug Monit 1999; 21:97-101.
7. Schou M. Forty years of lithium treatment. Arch Gen Psychiatry 1997; 54:9-15.
8. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. Br J Clin Pharmacol 2000; 49:303-12.
9. Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. Clin Chem 1998; 44:1073-84.
10. Cusin C, Serretti A, Mandelli L, Lucca A, Smeraldi E. Seasonal

variations of lithium plasma levels. Psychiatry Res 2002; 111:35-41.
11. Beersma DG, Dols LC, Mersch PP, den Boer JA, van den Hoofdakker RH. Lithium concentrations in plasma of lithium-treated psychiatric patients in the Netherlands: commentary on Cusin et al. Psychiatry Res 2002; 111:43-4.
12. D'Mello DA, McNeil JA, Msibi B. Seasons and bipolar disorder. Ann Clin Psychiatry 1995; 7:11-8.
13. Medhi B, Sukhija M, Sumedh G, et al. Lithium therapeutic drug monitoring pattern at a tertiary care hospital in India. JK Practitioner 2006; 13:15-7.
14. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002; 159(4 Suppl):1-50.
15. Vestergaard P, Licht RW, Brodersen A, et al. Outcome of lithium prophylaxis: a prospective follow-up of affective disorder patients assigned to high and low serum lithium levels. Acta Psychiatr Scand 1998; 98:310-5.
16. Shin K, Schaffer A, Levitt AJ, Boyle MH. Seasonality in a community sample of bipolar, unipolar and control subjects. J Affect Disord 2005; 86:19-25.
17. Morken G, Lilleeng S, Linaker OM. Seasonal variation in suicides and in admissions to hospital for mania and depression. J Affect Disord 2002; 69:39-45.
18. Clarke M, Moran P, Keogh F, et al. Seasonal influences on admissions for affective disorder and schizophrenia in Ireland: a comparison of first and readmissions. Eur Psychiatry 1999; 14: 251-5.
19. Shapira A, Shiloh R, Potchter O, et al. Admission rates of bipolar depressed patients increase during spring/summer and correlate with maximal environmental temperature. Bipolar Disord 2004; 6:90-3.
20. Maes M, Schotte C. Seasonal variation in postdexamethasone cortisol values in depressed inpatients. Results of least square cosine spectral analysis. J Affect Disord 1997; 44:5-12.
21. Maes M, Scharpe S, Verkerk R, et al. Seasonal variation in plasma L-tryptophan availability in healthy volunteers. Arch Gen Psychiatry 1995; 52:937-46.
22. Brewerton TD, Berrettini WH, Nurnberger JI, Linnoila M. Analysis of seasonal fluctuation of CSF monoamine metabolites and neuropeptides in normal controls: Findings with 5HIAA and HVA. Psychiatry Res 1988; 23:257-65.
23. Cappiello A, Malison RT, McDougle CJ, et al. Seasonal variation in neuroendocrine and mood responses to i.v. L-tryptophan in depressed patients and healthy subjects. Neuropsychopharmacology 1996; 15:475-83.
24. Joffe RT, Levitt AJ. Seasonal variation of peripheral thyroid hormone levels in major depression. J Affect Disord 1991; 23:49-51.
25. Greenspan K, Goodwin FK, Bunney WE, Durell J. Lithium ion retention and distribution. Patterns during acute mania and normothymia. Arch Gen Psychiatry 1968; 19:664-75.
26. Garver DL, Hutchinson LJ. Psychosis, lithium-induced antipsychotic response and seasonality. Psychiatry Res 1988; 26:279-86.