International Journal of Scientific Reports
Sarraf DP et al. Int J Sci Rep. 2021 Jul;7(7):340-345
http://www.sci-rep.com
pISSN 2454-2156 | eISSN 2454-2164
DOI: https://dx.doi.org/10.18203/issn.2454-2156.IntJSciRep20212392

Original Research Article

Pattern of adverse drug reactions and serum level of maintenance lithium treatment in patients with bipolar affective disorder: a cross-sectional study in Eastern Nepal

Deependra Prasad Sarraf[1]*, Suraj Nepal[2]

[1]Department of Clinical Pharmacology and Therapeutics, B. P. Koirala Institute of Health Sciences, Dharan, Nepal
[2]Department of Psychiatry, B. P. Koirala Institute of Health Sciences, Dharan, Nepal

Received: 17 May 2021
Accepted: 09 June 2021

***Correspondence:**
Dr. Deependra Prasad Sarraf,
E-mail: deependraprasadsarraf@gmail.com

ABSTRACT

Background: Benefits of lithium maintenance therapy in bipolar affective disorder (BPAD) are restricted by adverse drug reactions (ADRs) and low therapeutic index. The same dose of lithium has sub-therapeutic, therapeutic and supra-therapeutic serum level in different patients. The objective of this study was to describe the pattern of ADR and serum concentration of maintenance dose of lithium in patients with BPAD.
Methods: A cross-sectional study was conducted in patients diagnosed with BPAD and taking lithium monotherapy 900 mg daily at least for 6 months at outpatient department of psychiatry, B. P. Koirala institute of health sciences. Sociodemographic profile and relevant laboratory investigations were recorded on a self-designed proforma. Chi square test, ANOVA test and student's t test were used for analysing the data at p value <0.05.
Results: Out of 123, 64 (52.0%) were female. Serum concentration ranged from 0.31 to 1.51 mmol/l with mean of 0.803 mmol/l and was in therapeutic range in 104 (84.6%) patients. At least one ADR was seen in 81 (65.9%) patients and hand tremor (43.6%) was the commonest ADR. Hypothyroidism and hyperthyroidism were seen in 9 (6.8%) and 6 (4.5%) patients, respectively. Occurrence of ADRs were more in female and was significantly significant (P value <0.05).
Conclusions: The serum level of lithium 900 mg/day varied widely and was in therapeutic range in majority of the patients. Prevalence of ADRs was 65.9%. Occurrence of ADRs were significantly more common in female patients and supra-therapeutic serum concentration of lithium. A prospective long-term study should be conducted to validate the study findings.

Keywords: Adverse drug reactions, Bipolar affective disorder, Lithium, Eastern Nepal

INTRODUCTION

Bipolar affective disorder (BPAD) causes unusual shifts in mood, energy, activity levels and concentration. It affects about 2% of the world's population and causes periods of unusually intense emotion, changes in sleep patterns and activity levels which lasts for days to weeks. It usually requires lifelong treatment with a combination of medication and psychotherapy.[1] its treatment consists of acute stabilization of the patient to a symptomatic recovery with euthymic mood; then maintenance therapy is started to prevent relapse and to enhance social and occupational functioning of the patient. Lithium carbonate is the gold standard for the long-term maintenance of BPAD and has well established evidence of superior efficacy compared to other mood stabilizers.[2] compared to other mood stabilizers, lithium also exerts anti-suicidal, immunomodulatory and neuroprotective

effects.[3] However, the benefits of lithium are restricted by adverse drug reactions (ADRS) and a low therapeutic index.[4] ADR is also one of the important factor for nonadherence to long-term lithium therapy in more than 40% cases.[5] the main ADR of long-term treatment of lithium are generally related to thyroid, renal and cognitive function. As lithium has low therapeutic index, periodic laboratory tests are required to monitor its plasma concentration which help to assess the patient's response to it.

The maintenance dose of lithium ranges from 900 mg per day to 2400 mg per day which is administered in two to four divided doses.[6] the recommended serum level of lithium is 0.6-1.2 mmol/l for maintenance therapy in bpad.[7] the same dose of lithium has sub-therapeutic, therapeutic and supra-therapeutic serum level in different patients. Data on ADRS and serum concentration of maintenance dose of lithium in patients with BPAD is scarce in our context. Therefore, we aimed to describe the pattern of ADR and serum concentration of maintenance dose of lithium 900 mg per day in patients with BPAD.

METHODS

Study setting and design

A cross-sectional descriptive study was conducted among patients with BPAD at outpatient department (OPD) of psychiatry, B.P. Koirala Institute of Health Sciences, Dharan, Nepal from January to December 2019. The patients diagnosed with BPAD, having euthymic condition and taking lithium 900 mg/day as maintenance therapy for at least 6 months and those who were more than 17 years of age were enrolled in the study. Pregnant patients, taking other psychotropic drugs like benzodiazepines, antipsychotics, antidepressants and antianxiety drugs and those who did not give consent were excluded from the study. Convenience sampling method was used.

Data collection tool

A self-designed proforma was used to collect sociodemographic profile (name, age, sex, marital status, socioeconomic status, educational status, occupation), co-morbid conditions, laboratory investigations (urine re/me, urea/creatinine, thyroid function test and ECG), serum concentration of lithium and ADRS. Blood sample was taken 12 hours after evening dose of lithium and its concentration was measured through colorimetric test (roche/hitachi COBAS c 501 analyzer, Roche diagnostics, USA).

Data collection method

The objectives of the study were explained to the patients at the time of consultation in psychiatry OPD and written consent was taken. The relevant data were collected directly in the proforma by reviewing the health card of the patients. They were also interviewed for the adverse drug reactions they have experienced.

Statistical analysis

The data were entered into Microsoft excel 2007. Descriptive statistics mean, frequency, percentage and standard deviation (SD) were calculated. BMI (kg/m2) was categorized into underweight, normal weight, overweight and obese as per international guideline.8 serum concentration of lithium was also categorized as "below therapeutic level (<0.6 mmol/l)", "therapeutic level (0.6-1.2 mmol/l)" and "above therapeutic level (>1.2 mmol/l)". Chi-square test, anova and student's t test were used for analyzing the data. P-value <0.05 was considered as statistically significant. All statistical calculations were performed using SPSS version 11.0 (Chicago, USA).

RESULTS

A total of 123 patients participated. The age of the patients ranged from 18-60 years with mean age of 31.02 years (SD=9.6 years). Majority of patients were female (52%), married (65%) and Hindu (85.4%). Most of the patients (89.4%) were literate. Out of 123, 42 (34.1%) patients were overweight. Duration of lithium therapy ranged from 6 month to 6 year and 77 (62.6%) patients were taking lithium for 6-24 months (Table 1).

Serum lithium concentration ranged from 0.31 to 1.51 mmol/l with mean of 0.803 mmol/l (SD=0.197). It was in therapeutic range in 104 (84.6%) patients, sub-therapeutic in 15 (12.2%) and supra-therapeutic in 4 (3.3%) patients (Figure 1).

Serum concentration of lithium was high in those patients who were male, aged 18-45 years, other than Hindu religion, Mongolian and underweight. However, it was statistically not significant (P value >0.05) (Table 2).

Figure 2 shows the pattern of ADRs in the patients with BPAD and taking lithium 900 mg/day. A total of 133 ADRs were detected in 81 (65.9%) patients. Out of 81, 38 (46.9%) patients had single ADR followed by two ADRs in 33 (42.0%) patients and three ADRs in 9 (11.1%) patients. Hand tremor (43.6%) was the common ADR followed by nausea (11.3%) and leukocytosis (8.3%). Hypothyroidism and hyperthyroidism were seen in 9 (6.8%) and 6 (4.5%) patients respectively (Figure 2).

Occurrence of ADRs were significantly more common in female patients and supra-therapeutic serum concentration of lithium (P value <0.05) (Table 3).

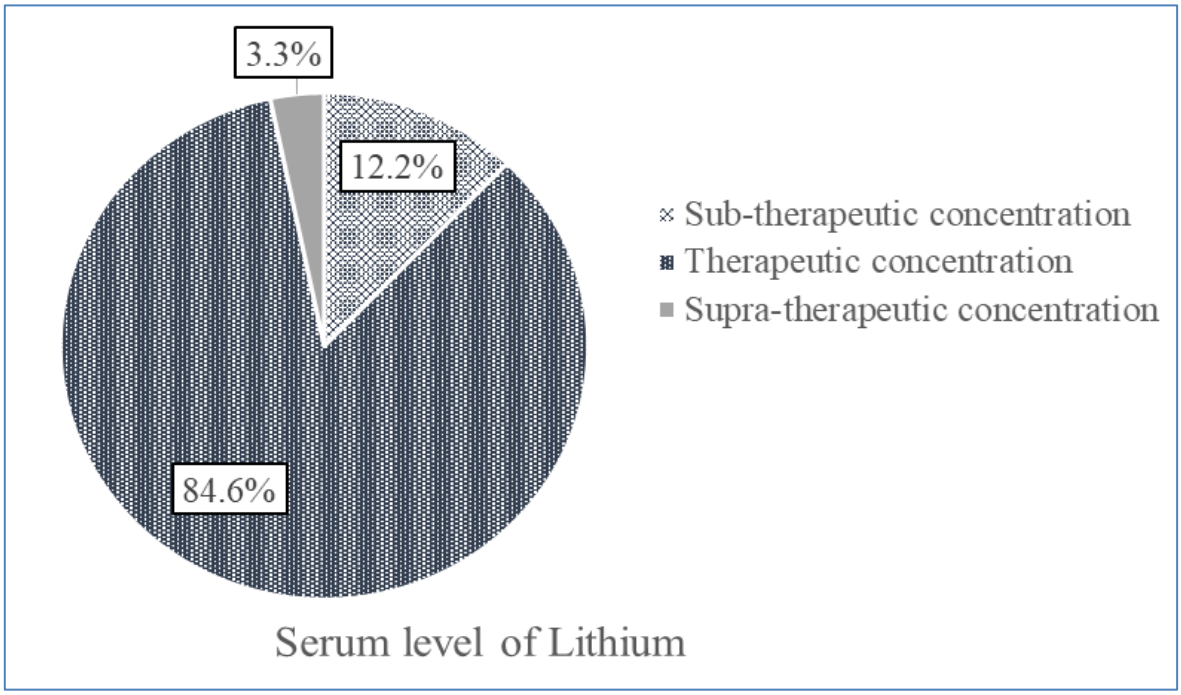

Figure 1: Category of serum level of lithium (n=123).

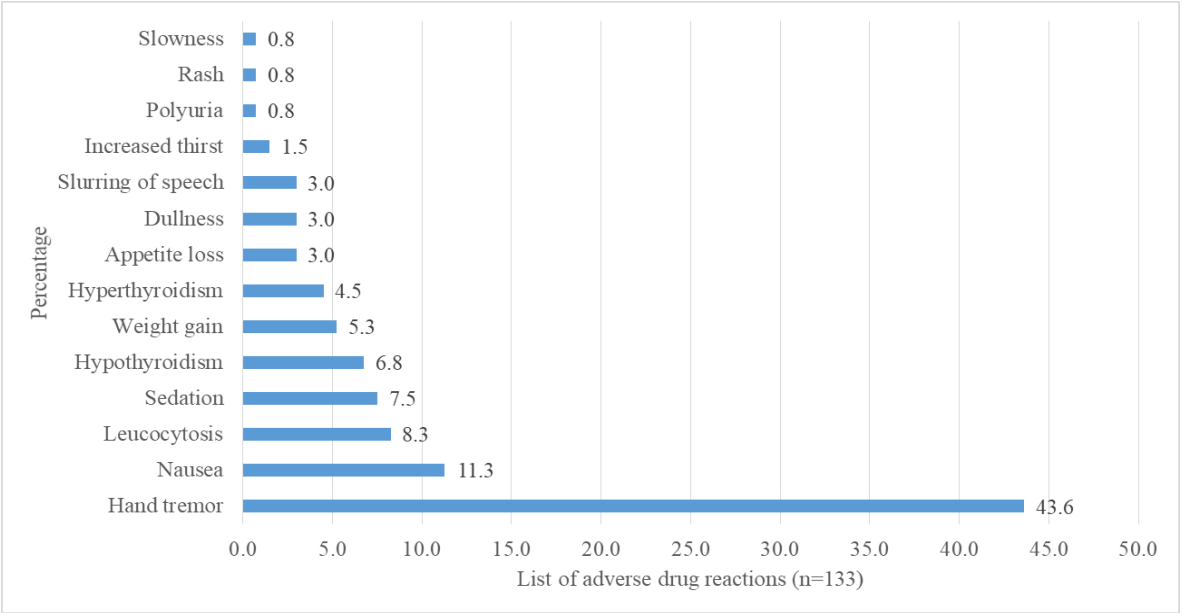

Figure 2: List of adverse drug reactions due to lithium monotherapy (n=133).

Table 1: Socio demographic characteristics of the patients (n=123).

Variables	Categories	Frequency	Percentage
Gender	Male	59	48
	Female	64	52
Age category (in years)	18-45	113	91.9
	More than 45	10	8.1
Marital status	Married	80	65
	Unmarried	38	30.9
	Others	5	4.1
Educational level	Illiterate	13	10.6

Continued.

Variables	Categories	Frequency	Percentage
	Literate	110	89.4
Religion	Hindu	105	85.4
	Others	18	14.6
Body mass index (kg/m^2)	Underweight	7	5.7
	Normal	51	41.5
	Overweight	42	34.1
	Obese	23	18.7
Duration of lithium therapy (in months)	6-24	77	62.6
	25-48	40	32.5
	49-72	6	4.9

Table 2: Effect of baseline variables on serum concentration of lithium (n=123).

Variables	Categories	Mean serum lithium concentration	SD	P value*
Gender	Male	0.806	0.197	0.719
	Female	0.800	0.198	
Age (in years)	18-45	0.803	0.199	0.979
	More than 45	0.802	0.180	
Religion	Hindu	0.799	0.192	0.681
	Others	0.826	0.230	
Race	Aryan	0.800	0.198	0.960
	Mongolian	0.816	0.198	
Body mass index (kg/m^2)**	Underweight	0.820	0.202	0.870
	Normal	0.815	0.209	
	Overweight	0.782	0.201	
	Obese	0.809	0.169	

*Statistically not significant at P value <0.05; **ANOVA test.

Table 3: Correlation of adverse drug reactions with baseline variables (n=123).

Variables	Categories	Adverse drug reactions		P value
		Present N (%)	**Absent N (%)**	
Gender	Male (N=59)	32 (54.2)	27 (45.8)	0.013*
	Female (N=64)	49 (76.6)	15 (23.4)	
Age (in years)	18-45 (N=113)	73 (64.6)	40 (35.4)	0.325
	More than 45 (N=10)	8 (80.0)	2 (20.0)	
Marital status	Married (N=80)	55 (68.8)	25 (31.3)	0.652
	Unmarried (N=38)	23 (60.5)	15 (39.5)	
	Others (N=5)	3 (60.0)	2 (40.0)	
Educational status	Literate (N=13)	10 (76.9)	3 (23.1)	0.373
	Illiterate (N=110)	71 (64.5)	39 (35.5)	
Religion	Hindu (N=105)	68 (64.8)	37 (35.2)	0.602
	Others (N=18)	13 (72.2)	5 (27.8)	
Race	Aryan (N=102)	66 (64.7)	36 (35.3)	0.622
	Mongolian (N=21)	15 (71.4)	6 (28.6)	
Body mass index (kg/m^2)	Underweight (N=7)	4 (57.1)	3 (42.9)	0.240
	Normal (N=51)	29 (56.9)	22 (43.1)	
	Overweight (N=42)	32 (76.2)	10 (23.8)	
	Obese (N=23)	16 (69.6)	7 (30.4)	
Serum lithium level	Sub-therapeutic concentration (N=15)	6 (40.0)	9 (60.0)	0.033*
	Therapeutic concentration (N=104)	71 (68.3)	33 (31.7)	
	Supra-therapeutic concentration (N=4)	4 (100.0)	0 (0.0)	

*Statistically significant at P value <0.05 (Chi square test).

DISCUSSION

Despite the fact that lithium is currently the first choice mood stabilizer for maintenance treatment of BPAD globally, its therapeutic index is low and it produces various adverse effects as a result of which patient compliance is less. In this study, pattern of serum level of lithium 900 mg/daily and associated ADRs were analyzed. Serum level of lithium varied widely (0.31-1.51 mmol/L) in this study and its level was in therapeutic range in majority of the patients. However, its level was sub-therapeutic in one out of ten (12.2%) patients. As the patient were in euthymic state, this study finding showed that even sub-therapeutic level of lithium was efficacious. It was interesting to find that serum level of lithium was high in those patients who were male, aged 18-45 years, other than Hindu religion, Mongolian and underweight, however, it was statistically not significant (P value >0.05). This finding was similar to a study by Nolen et al in which they did not find evidence addressing ethnicity or gender in relation to optimal lithium serum levels in patient with BPAD.[7] Due to its low therapeutic index, serum level of lithium should always be monitored during initiation of the treatment, after each dose increment and then every 3-6 months thereafter.[7]

Nearly two third of the patients had at least one ADR indicating high prevalence of ADRs. More than one third of the patients had two ADRs. Occurrence of ADRs were significantly more common in female patients and supra-therapeutic serum concentration of lithium (P value <0.05). Four out of ten patients had hand tremor in this study. In contrast, this was higher than other report in which one quarter of the patients treated with lithium had ADRs.[9] The lithium induced tremor often decreases with time. Changing the dose or preparation of lithium, reducing caffeine intake and decreasing or eliminating other drugs may also help the patients in case of distressing tremor. It can also be treated by beta-blockers like propranolol, primidone, fatty acids, vitamin B6, potassium or benzodiazepines. Lithium toxicity also presents with severe tremor and appropriate assessment of the patient is mandatory.[10]

Nausea was observed in one out of ten patients which was similar to other reports in which it occurred in 10-20% of lithium-treated patients.[10] Nausea is not much distressing to the patients; however, the patients can be counselled to take lithium after meals, using a multiple daily dose regimen or using sustained release preparations of lithium to diminish nausea. Tolerance to the nausea commonly occurs over time. Weight gain was reported by 5.3% of the patients in this study. In contrast, it was more prevalent in another report.[11] It is among the most distressing lithium-associated ADR that might result in patient non-compliance.[11] It is hypothesized that lithium causes weight gain by altering core mechanisms in the brain.[12] Hypothyroidism was present in 6.8% of the patients and this was similar to other report.[12] In another cross sectional study by Kirov et al the prevalence of hypothyroidism was higher (10.3%).[13] Inhibition of thyroid hormone release from the thyroid gland, decrease in iodine trapping and inhibition of synthesis of thyroid hormones are the some of the possible mechanism of lithium-induced hypothyroidism.[14,15] Due to this high frequency of hypothyroidism, it is clinically plausible to assess the thyroid function status, thyroid size and presence of thyroid auto-antibodies in all patients prior to initiation of lithium therapy and later annually.

A negative effect of lithium on cognition like dullness, slowness was also found in some patients which might lead to non-adherence to the therapy. Lithium-induced hypothyroidism may be partly responsible for these cognitive ADRs. Managing the ADRs related to lithium remains a critical element in optimal treatment of BPAD. Addressing treatment related ADRs in the patients taking maintenance lithium may ensure maximize clinical response.

Limitations

This study had some limitations. The sample size was small. As this study was conducted at a single center, the results could not be generalized. The effect of co-administered over-the-counter drugs and patient adherence on serum concentration of lithium could not be assessed. Causality and severity assessment of the ADRs could not be conducted. Compliance to the treatment could not be assessed.

CONCLUSION

The present study showed that serum level of lithium 900 mg/day varied widely and was in therapeutic range in majority of the patients. Being male, aged 18-45 years, other than Hindu religion, Mongolian race and underweight were identified as potential factors for having high serum level of lithium. Prevalence of ADRs was 65.9% and hand tremor was the common ADR. Hypothyroidism was more common than hyper-thyroidism. Occurrence of ADRs were significantly more common in female patients and supra-therapeutic serum concentration of lithium. Proper education and monitoring may diminish the number of ADRs in BPAD treated with lithium. A prospective long-term study should be conducted to validate the study findings.

ACKNOWLEDGEMENTS

We would like to thank Dr. Shashi Keshwar for reviewing the manuscript.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. National Institute of Mental Health. Fact sheet: Bipolar Disorder, 2021. Available at: https://www.nimh.nih.gov/health/topics/bipolar-disorder/ Accessed on 2 May 2020.
2. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672-82.
3. Ferensztajn-Rochowiak E, Chłopocka-Woźniak M, Rybakowski JK. Ultra-long-term lithium therapy: all-important matters and a case of successful 50-year lithium treatment. Braz J Psychiatry. 2020:1516-44462020005030204.
4. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379(9817):721-8.
5. Perlick DA, Rosen RA, Kaczynski R. Medication nonadherence in bipolar disorder: a patient-centered review of research findings. Clin Approaches Bipolar Disord. 2004;3:56-64.
6. Horton S, Tuerk A, Cook D, Cook J, Dhurjati P. Maximum recommended dosage of lithium for pregnant women based on a PBPK model for lithium absorption. Adv Bioinformat. 2012;2012:352729.
7. Nolen WA, Licht RW, Young AH, Malhi GS, Tohen M, Vieta E, et al. ISBD/IGSLI Task Force on the treatment with lithium. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord. 2019;21(5):394-409.
8. Lim JU, Lee JH, Kim JS, Hwang YI, Kim TH, Lim SY, et al. Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J Chron Obstruct Pulmon Dis. 2017;12:2465-75.
9. Gelenberg AJ, Jefferson JW. Lithium tremor. J Clin Psychiatry. 1995;56(7):283-7.
10. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord. 2016;4(1):27.
11. Gitlin MJ, Cochran SD, Jamison KR. Maintenance lithium treatment: side effects and compliance. J Clin Psychiatry. 1989;50(4):127-31.
12. Ackerman S, Nolan LJ. Body weight gain induced by psychotropic drugs: incidence, mechanisms and management. CNS Drugs. 1998;9:135-51.
13. Kleiner J, Altshuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. J Clin Psychiatry. 1999;60(4):249-55.
14. Kirov G, Tredget J, John R, Owen MJ, Lazarus JH. A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. J Affect Disord. 2005;87(2-3):313-7.
15. Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab. 2009;23(6):723-33.
16. Kibirige D, Luzinda K, Ssekitoleko R. Spectrum of lithium induced thyroid abnormalities: a current perspective. Thyroid Res. 2013;6(1):3.

Cite this article as: Sarraf DP, Nepal S. Pattern of adverse drug reactions and serum level of maintenance lithium treatment in patients with bipolar affective disorder: a cross-sectional study in Eastern Nepal. Int J Sci Rep 2021;7(7):340-5.