ORIGINAL ARTICLE

Association of Plasma Level of Lithium with Clinical Effect in Bipolar Disorder at a Tertiary Center in Eastern Nepal

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Abstract

Introduction: *Lithium is widely used as the gold standard for the treatment of acute and maintenance treatment of Bipolar Affective Disorder (BPAD). Its therapeutic benefits are restricted by several adverse drug reactions (ADR). Therefore, it is necessary to measure its serum concentration for optimal dosing and clinical response and to minimize toxicity. The objectives of the study were to correlate dose of Lithium with its serum concentration and serum concentration of lithium with clinical effect.*

Material And Method: *A cross sectional study was conducted in 213 patients presenting to psychiatric OPD, diagnosed with BPAD and taking Lithium monotherapy at least for 3 months. Data collection was done from 15th December 2018 to14th December 2019. Sociodemographic profile and relevant laboratory investigations were recorded on a self-designed proforma. Young Mania Rating Scale and Hamilton Rating Scale for Depression were applied for objective assessment of remission. Chi square test was used to correlate categorical data and ANOVA test was used for continuous data using SPSS at P-value of 0.05.*

Results: *Majority of patients were male (51.6%), married (62.4%), Hindu (86.9%) and in remission phase (92%). Dose of lithium was 300-1200 mg/day; serum concentration was 0.26 to 1.51mmol/L, was in therapeutic range in majority of the patients (82.6%) and was positively correlated with the dose of lithium (P-value <0.0001).*

Conclusion: *Lithium is very effective for maintenance therapy in BPAD with wide variation in dose and serum concentration. The dose of lithium should be guided both on the basis of clinical assessment and serum concentration.*

Keywords: Bipolar affective disorder, Lithium, Serum concentration

INTRODUCTION

Bipolar affective disorder (BPAD) is characterized by episodes of hypomania, mania and mixed episodes with or without depressive episodes, with inter-episodic recovery. Lithium is used as the gold standard for the treatment of acute episodes and maintenance treatment of BPAD.[1,2] It has a narrow therapeutic range and therefore both its efficacy and toxicity are dose-dependent and therefore the margin between toxic, therapeutic and sub-therapeutic serum levels are liable to be crossed.[3] A number of factors like genetics, age, gender, ethnicity, nutritional status, smoking, comorbid disease and drug interactions affect metabolism and clearance of lithium.[4-6]

The optimal serum level of lithium for the prevention and treatment of BAPD is still unclear.[7]It has been observed that lithium frequently produces toxic effects in Nepalese patients at usual recommended dose of lithium. Most of Nepalese patients have toxic effects even at serum concentration of 0.6 to 1.2 mmol/L and at this dose there are minimal toxic effect in western patients.[8] There is paucity of reports on relationship between concentration of lithium and its clinical response in Nepalese population. Evidence to support the efficacy of

lithium at lower serum concentrations in Nepalese patients is also lacking.Therefore, this study wasconducted to correlate dose of Lithium with serum concentration of lithium and the serum concentration of lithium with clinical effect.

MATERIAL AND METHOD

A cross-sectional prospective study was conducted among patients having BPAD at Outpatient department of Psychiatry, B.P.Koirala Institute of Health Sciences, Dharan, Nepal from 15th December 2018 to 14th December 2019. Patients diagnosed with BPAD and taking lithium as monotherapy for at least 3 months were enrolled. Pregnant patients, taking other psychotropic drugs like Benzodiazepines, antipsychotics, antidepressants and antianxiety drugs, patients not giving consent were excluded.

A self-designed proforma was used to collect sociodemographic profile(name, age, sex, marital status, socioeconomic status, educational status), weight, height, co-morbid conditions, laboratory investigations (Urine RE/ME, urea/creatinine, Thyroid function test and ECG), drugs prescribed (name, dose, duration) and serum concentration of lithium. 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). The Young Mania Rating Scale (YMRS) isa validated and reliable tool to assess bipolar manic symptoms.[9]It has 11-item. Thepatients having YMRS score zero were designated as being in remission phase.Hamilton Depression Rating Scale (HDRS) is a validated and reliable tool to assess the depression in BPAD. It has 17-item.[10]Thepatients having HDRS score 7 or less were designated as being in remission phase.

The objectives of the study were explained to the eligible patients at the time of consultation in psychiatry outpatient department and written consent was taken. The relevant data were collected directly in the proforma by reviewing the health card of the patients and by face-to-face interview.The questionnaire were first prepared in English language and then translated in Nepali language by a separate translator and it was back-translated to English by an independent translator. The Nepali version was used to collect the relevant data. The questionnaire was pilot tested in 22 patients to validate it and those patients were not included in the analysis. The study was approved by Institutional Review Committee (IRC/1263/018), BPKIHS, Dharan, Nepal.

The data were entered into MS-Excel 2007. Descriptive statistics mean, frequency, percentage and SD were calculated.Basal metabolic index (Kg/m^2) was calculated and categorized into underweight, normal weight, overweight and obese as per international guideline.[26]Serum concentration of lithium was also categorized as "Below therapeutic level (<0.6mmol/L)", "Therapeutic level (0.6-1.2mmol/L)" and "Above therapeutic level (>1.2mmol/L)".[11]ANOVA test, Student t test, and Spearman's rho correlation test was used for analyzing non-categorical data and Chi-square test for categorical data. P-value <0.05 was considered as statistically significant. All statistical calculations were performed using SPSS version 11.0 (Chicago, USA).

RESULT

Out of 213 patients, majority were male (51.6%), married (62.4%), Hindu (86.9%), Aryan (80.3%) and in 3rd to 4th decade of their life (63.4%). Most of the patients (47.4%) had completed secondary level of education.Sixty nine (32.4%) patients were substance user (**Table 1**). Eight patients (3.8%) had comorbidities and hypertension (50%) was the commonest comorbidity followed by diabetes mellitus (25%) and mental retardation (25%).Urine RE/ME, Renal function test (serum urea and creatinine) and ECG were within normal limits in all patients.

Table 2 represents the descriptive data of the patients. Mean age of the patients was 32.06±10.80 years. Mean duration of lithium (Li) therapy was 27.78±16.24 months (Table 2).

More than one third of the patients (37.1%) were taking lithium for 13-24 months followed by 6-12 months (21.1%) (Figure 1).

Most of the patients (42.3%) had normal weight and 30.5% were overweight (Figure 2)

Age had negative correlation with serum level of lithium; however it was statistically not significant (P-value >0.05). Similarly Serum level of lithium had positive correlation with BMI, duration of lithium therapy and dose of the lithium; however it was statistically

significantonly with the dose (P-value >0.05). (Table 3).

Table 1: Socio demographic characteristics of the patients (n=213)

Variables	Categories	Number of patients	Percentage
Gender	Male	110	51.6
	Female	103	48.4
Age category (years)	12 – 20	32	15
	21 – 30	76	35.7
	31 – 40	59	27.7
	41 – 50	34	16
	>60	12	5.6
Marital status	Married	133	62.4
	Unmarried	70	32.9
	Divorced	7	3.3
	Widow	3	1.4
Socioeconomic status	Low	96	45.1
	Low middle	62	29.1
	Middle	55	25.8
Educational level	Illiterate	19	8.9
	Primary	45	21.1
	Secondary	101	47.4
	Higher secondary	34	16
	Bachelor and above	14	6.6
Religion	Hindu	185	86.9
	Christian	10	4.7
	Kirat	8	3.8
	Muslim	7	3.3
	Buddhist	3	1.4
Race	Aryan	171	80.3
	Mongolian	42	19.7
Substance user	Yes	69	32.4
	No	144	67.6

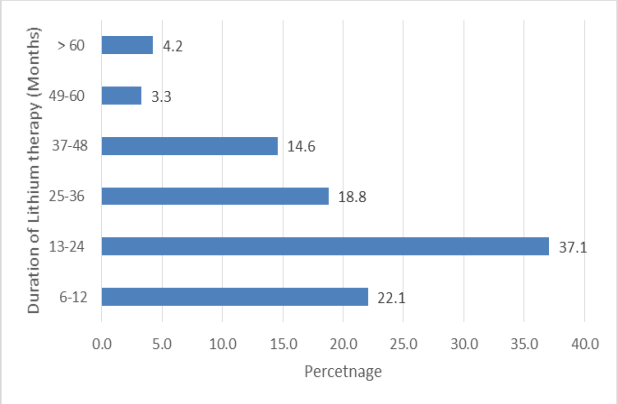

Figure 1: Duration of Lithium therapy in years (n=213)

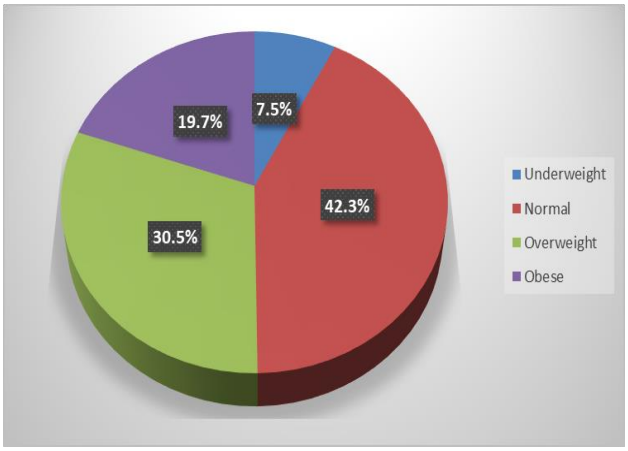

Figure 2: Category of BMI (kg/m2) of the patients (n=213)

Table 2: Descriptive statistics of the patients (n=213)

Variables	Mean	SD	Median	Mode	Minimum	Maximum
Age in years	23.06	10.805	30	28	12	72
Body Mass Index in Kg/m²	22.65	2.99	23	21	16	34.4
Duration on lithium therapy in months	27.78	16.244	23	21	6	96
Dose of lithium in mg/day	891.9	152.69	900	900	300	1200
Serum level of lithium inmmol/L	0.800	0.211	0.800	0.800	0.26	1.51

Table 3: Correlation of Serum lithium level with age, BMI, duration of lithium therapy and dose (n=213)

Variable	Serum level of Lithium	
	Pearson's coefficient (r)	P-value
Age	-0.08	0.242
BMI	0.024	0.732
Duration of lithium therapy	0.085	0.218$
Dose of the lithium	0.469	<0.001*

$Spearman's rho correlation test
**Statistically significant (Pearson Correlation test)*

More than half of the patients (57.7%) were prescribed 900mg lithium per day followed by 1050mg/day (18.8%). Dose of lithium ranged from 300 to 1200 mg/day. Serum concentration of lithium ranged from 0.26 to 1.51mmol/L (**Table 4**).

Serum concentration of lithium was therapeutic in most of the patients (82.6%) followed by sub-therapeutic (14.1%) (Figure 3).

Figure 4 represents the line diagram of concentration of lithium at various doses and it signifies that concentration is non-linear with the dose prescribed.

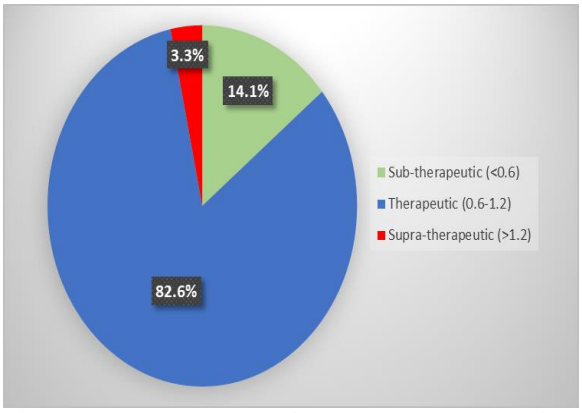

Figure 3: Category of serum concentration (mmol/L) of Lithium in the patients (n=213)

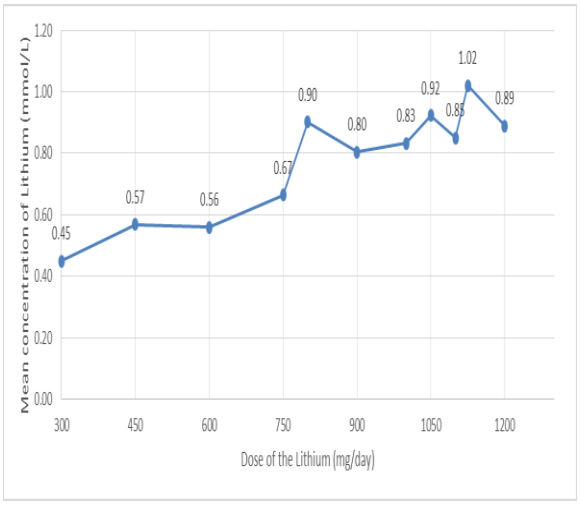

Figure 4: Line diagram of mean serum concentration of Lithium and its dose per day

Table 4: Serum level of Lithium at each dose (n=213)

Lithium dose (mg/day)	Number of Patients	Serum concentration of Lithium (mmol/L)	Mean±SD (mmol/L)	Below therapeutic range (<0.6mmol/L)	Therapeutic range (0.6-1.2 mmol/L)	Above therapeutic range (>1.2mmol/L)
300	1	0.41	-	1	0	0
450	8	0.45-0.6	0.568±0.053	3	5	0
600	14	0.26-0.9	0.561±0.176	5	9	0
750	6	0.5-0.7	0.665±0.125	2	4	0
800	9	0.65-1.0	0.801±0.120	0	9	0
900	123	0.31-1.51	0.803±0.197	15	104	4
1000	4	0.55-1.2	0.832±0.319	2	2	0
1050	40	0.54-1.4	0.923±0.182	2	35	3
1100	1	0.85	-	0	1	0
1125	3	0.75-1.18	1.02±0.235	0	3	0
1200	4	0.67-1.1	0.890±0.195	0	4	0

Table 5: Correlation of Clinico-demographic variables with serum lithium concentration

Variables		Mean serum concentration of lithium± SD	P-value
Gender	Male	0.816±0.208	0.261
	Female	0.784±0.214	
Marital status	Married	0.804±0.196	0.510
	Unmarried	0.806±0.228	
	Divorced	0.834±0.256	
	Single	0.466±0.162	
Age category (years)	12 – 20	0.772±0.221	0.299
	21 – 30	0.824±0.199	
	31 – 40	0.806±0.211	
	41 – 50	0.804±0.234	
	>60	0.690±0.183	
Religion	Hindu	0.795±0.211	0.461
	Muslim	0.875±0.252	
	Buddhist	0.740±0.165	
	Christian	0.773±0.250	
	Kirat	0.912±0.121	
Race	Aryan	0.796±0.211	0.581
	Mongolian	0.817±0.213	
Socioeconomic status	Low	0.813±0.199	0.275
	Low middle	0.764±0.202	
	Middle	0.819±0.238	
Educational level	Illiterate	0.746±0.220	0.358
	Primary	0.783±0.205	
	Secondary	0.795±0.203	
	Higher secondary	0.859±0.166	
	Bachelor and above	0.826±0.338	
Comorbidities	Yes	0.741±0.291	0.417
	No	0.803±0.208	
Taking other drugs	Yes	0.710±0.269	0.454
	No	0.802±0.211	
Substance user	Yes	0.775±0.203	0.220
	No	0.813± 0.214	
Duration of lithium therapy (months)	6 – 12	0.778±0.228	0.771
	13 – 24	0.789±0.200	
	25 – 36	0.820±0.186	
	37 – 48	0.845±0.238	
	49 – 60	0.778±0.221	
	>60	0.796±0.241	
BMI	Underweight	0.775±0.200	0.889
	Normal weight	0.799±0.215	
	Overweight	0.815±0.226	
	Obese	0.792±0.186	

Serum concentration of lithium was high in those patients who were male, divorced, aged 21-30 years, Kirat, Mongolian, overweight, substance user, having comorbidities, taking other drugs, completed higher secondary education, middle socioeconomic status and duration of therapy having 37-48 months; however, it was statistically not significant (P-value >0.005) (**Table 5**).

YMRS and HDRS score showed that out of 213 patients, 196 patients (92%) were in remission phase and it was observed in all category of serum concentration (Therapeutic, Below and Above therapeutic) of lithium; however, it was statistically not significant (P-value>0.005) (**Table 6**).

Table 6: Correlation of serum concentration of lithium with remission

Serum concentration of Lithium	Remission		P-value
	Yes	No	
Below therapeutic	28	2	0.688
Therapeutic	161	15	
Above therapeutic	7	0	

DISCUSSION:

Our study provides statistical evidence of positive relationship between the prescribed dose and serum concentration of lithium and similar results had been demonstrated by Bhandari et al and Lamichhane et al.[12,13]It is better to follow the guidelines and have therapeutic drug monitoring of lithium before increasing its dose; otherwise there may be attainment of toxic level of lithium in some patients. Male to female ratio was almost equal to 1 in our study. Higher number of male had BPAD in other study.[12,14]However, most studies report an almost equal gender ratio in the prevalence of BPAD.[15]Majority of the patients were in 3rdand 4th decade of their life with mean age of 32.06±10.80 years. A higher mean age (37.46±1.54) was reported in other studies.[3,14]BPAD is a chronic mental illness with the peak age of onset between 20 and 40 years.[16]These group of patients may have more stressful life as compared to others.Most of the patient had low SES in our study. Similar distribution of BPAD was seen in other studies.[17]Tsuchiya et al has suggested that BPAD is more common in low income, unemployed and unmarried groups of people.[18] Nearly one third of the patients were substance

user. Substance abuse is particularly common in BPAD and its co-occurrence often leads to a more pernicious and difficult to treat course of illness.[19]Mean BMI was 22.65 Kg/m^2 in our study. In contrast to this, mean BMI was higher (24.96 Kg/m^2) in a study by Lamichhane N et al.[12]Dose of lithium ranged from 300 to 1200 mg/day and mean dose was 891.9 mg and similar results had been reported in other study.[12] In contrast to this, 600mg was the minimum dose of lithium in an Indian study.[13]

Minimum effective serum level of lithium was 0.26 mmol/L in our study. In contrast to this, minimum effective serum concentration of lithium was 0.16 mmol/L in a study by Lamichhane N et al.[12]A higher minimal efficacious serum level (0.4 and 0.39mmol/L) was reported in other studies.[7,13] The guidelines has suggested that serum level of 0.6-0.8 mmol/L is optimum for prophylaxis of BPAD which is higher than our findings.[2]Most clinicians advocate a serum concentration of 0.8-1.2 mEq/L during initial treatment of acute mania.[20] Some patients may require serum lithium concentrations outside the usual ranges. For instance, elderly patients may require lower levels.

Mean serum concentration was 0.800±0.211 mmol/Lin our study. Lamichhane et al had reported a lower mean serum level of lithium (0.596 ±0.211 mmol/L) in their study.[12] Interindividual variation in pharmacokinetics and pharmacodynamics, as well as such external factors as diet and concomitant medications can affect serum lithium levels.[21]Therefore it is better to choose the dose of lithium based on individual patients' characteristics in BPAD.

Majority of the patients had serum concentration of lithium in therapeutic level in our study and similar results had been reported by Sharma et al.[22]Serum therapeutic level was out of therapeutic range in 17.4% patients in our study and was similar to the report of Sharma et al.[22]In contrast to this, it was out of therapeutic range in 44.6% patients in a study conducted in Thailand.[23]One third of the patients had sub-therapeutic level of lithium in a study by Marcus et al.[24]Remission was seen in all category of serum concentration (Therapeutic, Below/Above therapeutic) of lithium in our study. Randomized clinical trials are needed to establish therapeutic serum level of lithium in Nepalese population.

Lithium monotherapy was effective in BPAD in all age group in our study. It is beneficial to use the lowest possible dose of lithium to prevent immediate and long-term ADR in a patient who is on long-term maintenance therapy. The same brand of lithium should always be prescribed in BPAD as different preparations of lithium vary in bioavailability. Care should be taken, including additional monitoring, of changing between brands. Potential organ toxicity due to chronic lithium therapy requires more vigilance.

Limitations: Our study has some limitations. Calcium level was not checked in spite of hyperthyroidism being an ADR of lithium therapy. Effect of different brands of lithium on its serum concentration were not evaluated. Patient compliance to the prescribed lithium could not be assessed.

CONCLUSION:

Within the limitation of our study, the study findings showed that the lithium is very effective for maintenance therapy in BPAD at various doses. There is wide variation in its maintenance dose and serum concentration. Dose of the lithium should be guided both on the basis of clinical assessment and serum concentration. The serum concentration of lithium is inversely related with age and hence its maintenance dose should be less in young and elderly patients as compared to middle aged patients.

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