

## EFFECT OF LITHIUM THERAPY ON THYROID FUNCTION: A RETROSPECTIVE STUDY ON INDIAN PATIENTS

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### SUMMARY

*Thirty patients with Bipolar affective disorder who were on Lithium therapy for 6 months to 24 months, were tested for any alteration in their thyroid function. Eight (26.67%) patients had elevated serum TSH level and four (13.33%) patients had decreased serum T4 level than the normal range. Serum T3, although showing a declining trend, was found within the normal range in all the patients.*

The chance discovery of lithium's psychoactive properties by the Australian psychiatrist, John Cade in 1949 echoed the beginning of a new era in the treatment of mental disorders. Today, lithium is one of the major therapeutic appliances used by psychiatrists the world over in the treatment of Manic Depressive Psychoses. It has established its efficacy as a prophylactic agent for preventing future manic and depressive relapses. Among the various side effects recognized during the course of lithium therapy, one of the major ones was the development of various types of thyroid abnormalities. Goiter was recognized first (Schou et al, 1968; Fieve & Platman, 1968) followed by various reports of patients developing overt hypothyroidism (Wigger, 1968; Sedvall et al, 1968; Shopson et al, 1969) and hypothyroidism (Villeneuve et al, 1973). Reus et al (1979) reported hyperthyroidism and thyrotoxicosis following lithium therapy. Kuruvilla et al (1983) reported no change in thyroid function.

Recently Bocchetta et al (1991) reported visible and/or palpable goiter in 51% and subclinical hypothyroidism in 19% of patients. They also reported thyroid antibodies in 15% of lithium treated patients. The prevalence of specific antithyroid antibodies was higher in women and correlated positively with age and duration of lithium treatment. In another 2 year follow up study, Bocchetta et al (1992) observed that elevated thyroid stimulating hormone (TSH) concentrations were transitory in most patients except those with serum antithyroid antibodies. Those patients who initially had microsomal antibodies remained positive with an increase in titre in two-third of cases. They reported a higher risk of developing hypothyroidism in women, especially in presence of antibodies.

Little work has been done in India to find out the effect of lithium therapy on thyroid function in Indian patients. Kuruvilla et al (1983) had conducted a study which did not reveal any change in thyroid function after long term lithium therapy. The present study was conducted at S.S. Hospital, attached to Department of Psychiatry, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, with the following aims:

1. To study the clinical effect of lithium therapy on thyroid function in case of major affective disorder (bipolar).
2. To compare the effect of lithium therapy on thyroid function with age and sex matched controls of major affective disorder (bipolar) who were not on lithium therapy but were receiving other antipsychotic drugs.
3. To find out correlation between duration of lithium

- therapy and serum T<sub>3</sub>, T<sub>4</sub> & TSH levels.
4. To find out correlation between dose of lithium and serum T<sub>3</sub>, T<sub>4</sub> & TSH levels.
5. To find out correlation between serum lithium levels and serum T<sub>3</sub>, T<sub>4</sub> & TSH levels.

### METHOD

The study was conducted over a period of one year (January to December 1988) and informed consent was taken in each case, explaining the nature of the test. Only patients with Major Affective Disorder (Bipolar) who fulfilled the diagnostic criteria according to DSM III (American Psychiatric Association, 1980) were included in the study. Thirty patients who were only on prophylactic Lithium therapy for 6 months to 24 months and were euthymic for at least two months, were compared with age and sex matched controls. The controls consisted of 30 patients with major affective disorder who were euthymic for at least two months and were on antipsychotic therapy but not on lithium.

Patients with a history of any associated physical illness, history of irregular lithium therapy or having stopped lithium at any time during their maintenance, serum lithium levels lower or higher than prophylactic range i.e. 0.6 meq/L to 1.2 meq/L (Wolpert, 1980) were excluded from the study. Female patients were specially screened for pregnancy; those who were pregnant or who had amenorrhoea for more than 4 weeks were excluded from the study. A special precaution was taken for the history of intake of drugs which alter thyroid function e.g. thiocyanates and perchlorates, PAS, sulphonylureas, phenylbutazone, liquid I<sub>2</sub>, carbamazepine, steroids etc.

Thorough physical examination with special reference to clinical assessment of the thyroid was done in each patient. Thyroid hormone profile of both study and control groups was assessed by measuring serum T<sub>3</sub>, T<sub>4</sub> and TSH levels by Radioimmunoassay technique. The serum Lithium levels of patients in the study group were estimated by the method described by Amdisen (1967), using a digital flame and emission photometer.

### RESULTS

Patients were between the ages of 21 and 50 (mean 34.4 years); 50% between 31-40 years, 43.3% between 21-30 and 6.7% between 41-50 years. There were 25 (83.3%)

men and 5 (16.7%) women. The majority of patients (50%; M=43.3%; F=6.6%) were on lithium therapy for more than 6 to 12 months; Thirty percent were on lithium for 12 to 18 months and twenty percent on lithium for 18 to 24 months. The mean duration of lithium therapy was 14.17 months.

The largest group (50%; M=46.7%, F=3.3%) was formed by the patients who received 900 mg of lithium carbonate per day; 23.3% were on 600 mg, 16.7% on 750 mg, 6.7% on 1050 mg and 3.3% received 1200 mg of lithium carbonate per day. Forty percent (M=30%, F=10%) patients were in the dose range of 600-750 mg/day while 60% (M=53.3%, F=6.7%) were in the dose range of 700-1200 mg/day. The mean dose was 824 mg/day.

In the majority (40%) of the patients, serum level of lithium was 0.6 meq/L; it was 0.7 meq/L in 23.3%, 0.8 meq/L in 26.7% and 0.9 meq/L in 10% of patients. Sixty three percent had serum lithium levels in the range of 0.7-0.8 meq/L and 36.7% had between 0.8-0.9 meq/L.

The estimation of thyroid hormone profile revealed decreased serum T<sub>4</sub> levels in 4 (13.3%) patients and increased serum TSH levels in 8 (26.7%) patients (Table 1). Although the value of serum T<sub>3</sub> was within the normal range in all patients of the study group, it showed a

in study group and control group was statistically significant (Table 2).

A positive correlation was found between the duration of lithium therapy and serum TSH level. The correlation coefficient between duration of lithium therapy and serum T<sub>3</sub> and T<sub>4</sub> levels was negative. Similarly, a positive correlation was found between serum lithium and serum TSH whereas a negative correlation was found between serum lithium and serum T<sub>3</sub> and T<sub>4</sub>. However, none of the correlation coefficients were statistically significant.

## DISCUSSION

This study was conducted to find out the effect of lithium therapy on thyroid function. There was a male preponderance of 5:1 in the study group. Kuruvilla et al (1983) also reported a preponderance of males in their study (3:1). The majority of the patients (63.33%) were having Serum Lithium levels in the range of 0.6 to 0.7 meq/L, mean being 0.7 meq/L. This is in concordance with the findings of Maarbjerg et al (1987) who reported average serum lithium of 0.69 meq/L.

In earlier studies (Schou et al, 1968; Brownlie et al, 1976) it was found that patients who were on lithium therapy developed altered thyroid functions. Goiter was reported by Schou et al (1968) while Brownlie et al (1976) reported 14 cases of hypothyroidism and 4 cases of thyrotoxicosis. None of the patients in the study group had any evidence of thyroid swelling or goiter. Other observers (Sedvall et al, 1969; Cooper et al, 1969; Myers et al, 1985) also have not reported development of goiter despite longterm lithium use. Any clinical evidence of hyperthyroidism or thyrotoxicosis was not found in any of the patients of the study group, although cases of thyrotoxicosis have also been reported during lithium therapy without an obvious reduction in the dosage or serum level of lithium (Rosser, 1976; Cubbett, 1967).

The hormone profile of 8 patients (26.7%) of the study group revealed elevated serum TSH levels above the normal range (0.25 - 4 mIU/L). McLarz et al (1975), Emerson et al (1973) and Lazarus et al (1981) also reported elevation of basal TSH in 15.3% of patients on lithium therapy. Serum T<sub>4</sub> was found to be reduced below the normal range (6-14 mg%) in 4 patients (13.3%). Reduction in serum T<sub>4</sub> values in patients on lithium has also been reported by Emerson et al (1973) and Hufllin et al (1975).

When serum T<sub>3</sub>, T<sub>4</sub> and TSH levels were compared between patients in the study and control group, there was a decreasing trend in T<sub>3</sub> and T<sub>4</sub> towards the lower side of the normal range in patients of study group, although the difference was not statistically significant. The comparison of serum TSH level in patients of study and control groups showed an increasing trend towards the higher side of the normal range in study group and the difference was statistically significant. The comparison of serum T<sub>3</sub>, T<sub>4</sub> and TSH between male and female patients of study group did not show significant difference between male and female, although Crow et al (1973) reported that the

TABLE 1

Comparison of serum T<sub>4</sub> and serum TSH levels in patients of study and control groups (based on standard laboratory values)

	Total No.	Serum T <sub>4</sub>		Serum TSH			
		WNR No.	%	<NR No.	%	WNR No.	>NR No.
Study	30	26	86.7	4	13.3	22	73.3
Controls	30	30	100	-	-	30	100

[WNR: Within normal range; >NR: Higher than normal range; < NR: Lower than normal range]

Normal range:

Serum T<sub>3</sub>: 0.4 to 2 ng/ml

Serum TSH: 0.25 to 4 mIU/L

Serum T<sub>4</sub>: 6 to 14 µg %

TABLE 2

Comparison of serum T<sub>3</sub>, T<sub>4</sub> and TSH level in patients of study and control group (based on statistical analysis)

Variable	Study gp. (n=30) Mean SD (Range -)	Control gp. (n=30) Mean SD (Range -)	t	p
T <sub>3</sub> (ng/ml)	0.9 ± 0.37 (0.5 to 1.8)	0.97 ± 0.32 (0.6 to 1.6)	0.78	>0.4
T <sub>4</sub> (µg%)	9.36 ± 2.67 (4 to 11.6)	11.38 ± 2.17 (8 to 12.4)	0.22	>0.8
TSH (mIU/L)	3.03 ± 1.96 (0.28 to 7.4)	1.94 ± 0.75 (1.4 to 3.24)	2.81	*

\* Significant (p < 0.01)

declining trend towards the lower side of the normal range. On comparison, the difference between serum TSH levels

changes are more in females than males.

Simple correlation coefficient (r) between the duration of lithium therapy and serum T<sub>3</sub>, T<sub>4</sub> and TSH was found to be negative for serum T<sub>3</sub> & T<sub>4</sub> and positive for serum TSH. Similarly, simple correlation coefficient (r) between dose of lithium per day and serum T<sub>3</sub>, T<sub>4</sub> and TSH showed a negative correlation between the dose of lithium and serum T<sub>3</sub> & T<sub>4</sub> and a positive correlation with serum TSH. The correlation coefficient between serum lithium and serum T<sub>3</sub>, T<sub>4</sub> was negative while correlation coefficient between serum lithium and serum TSH was positive. The correlation of dose, duration and serum level of lithium with serum T<sub>3</sub>, T<sub>4</sub> and TSH levels indicates that higher dose, longer duration and higher serum levels of lithium increase the probability of reduction of thyroid hormone status of patients on lithium.

### CONCLUSION

Development of various types of thyroid abnormalities have been reported during the course of lithium therapy: goiter by Schou et al (1978), hypothyroidism by Wigger (1968), Sedvall et al, (1968) and hyperthyroidism and thyrotoxicosis by Reus et al (1979). Kuruvilla et al (1983) reported no change in thyroid function. The present study conducted on Indian patients, fulfilling DSM-III criteria for Major Affective Disorder (bipolar) on prophylactic lithium therapy for 6 to 24 months revealed changes in the thyroid hormone profile of these patients. These changes are suggestive of increased serum TSH and decreased serum T<sub>3</sub> and T<sub>4</sub> levels in patients of lithium therapy, although no clinical evidence of hypothyroidism could be detected.

If these patients are followed up for longer duration, it is quite likely that they may develop signs and symptoms of clinical hypothyroidism. This suggests that the thyroid hormone status must be screened at regular intervals in patients on lithium therapy.

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