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A STUDY OF SIDE EFFECTS OF LITHIUM

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SUMMARY

The present report is a study on the side effects experienced by the patients attending the Lithium Clinic of the Institute of Psychiatry, Government Rajaji Hospital, Madurai. Out of the 120 (M 78, F42) patients studied, 97 had side effects. The effects were examined in respect of their frequency, time of onset and course, their relation to the dose and serum levels of lithium and to the clinical response. The duration of therapy ranged from 3 months to 6 years.

The most frequent side effects were tremors (26.6%) and polyuria (20.8%).

The side effects occurred at varying periods from the onset of therapy. During the first 3 months, tremors, excess salivation, nausea and abdominal discomfort; weight gain, memory defects and polyuria, between 3 months and 1 year; and hypothyroidism, tardive dyskinesia, acne and hair fall beyond one year.

Lithium, the most preferred agent in prophylaxis of manic depressive psychosis has been an extensively studied drug in Psychiatry. It is to mood disorders what antibiotics are to infections. Lithium exerts numerous effects on the psysiological systems. Some of these are directly or indirectly related to its psychotropic action and also cause side effects during therapy. Side effects, mostly somatic, are quite common with lithium as with other psychotropic drugs (NIMH Report, 1970 ; Christodoulou et al., 1977; Fieve 1979). While some occur early and are transient, others appear later, tending to persist.

The present communication is a report on the side effects experienced by the patients observed in the Lithium Clinic of the Madurai Medical College and Government Rajaji Hospital, Madurai, India, during the last seven years. Earlier publications from this clinic include studies on clinical response to lithium (Venkoba Rao and Hariharasubramanian, 1978; Venkoba Rao et al., 1982 (a) and 1982 (b)) on electrolyte changes, changes in ECG, changes in renal structure and functions and on memory defects (Venkoba Rao et al., 1979, 1981; Venkoba Rao and Hariharasubramanian, 1980; Hariharasubramanian et al., 1978; Srinivasan et al., 1978; Sugumar et al., 1980).

AIM, MATERIAL AND METHOD

The present study examines the side effects of lithium in respect of their frequency, time of onset and course, their relation to the dose and serum levels of lithium and to the clinical symptomatology of 120 patients (Male-78, Female-42) who form the material for the study. The side effects noticed in the earlier patients in the clinic have been reported elsewhere (Venkoba Rao and Hariharasubramanian 1978; Venkoba Rao et al 1982a). The age of the patients ranged from 21-63 years (Mean : 39.5) (Bipolars-113, Unipolar manics-3, Unipolar depressives-4). The oral dose of lithium ranged from 750-1000 mgm/day and the serum lithium, periodically estimated, was in the range of 0.6—1.2 mmols/litre. The duration of therapy ranged from 3 months

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to 6 years. The patients received in addition, phenothiazines and tricyclics occasionally.

OBSERVATIONS

The side effects are listed in order of frequency of occurrence in Table I. Of the 120 patients, 97 had side effects (80.8%) while 23 had no side effects so far. More than one symptom was reported by 17 (14.2%). The side effects relate to neuromuscular and CNS (Tremores, memory defects, gait, tardive dyskinesia), gastro intestinal (nausea, abdominal discomfort, loose bowels, excess salivation), endocrine and metabolic systems (hypothyroidism, weight gain), water balance (polyuria/polydipsia) and skin (acne, fall of hair).

TABLE I—*Frequency of Side Effects.*

No. of patients studied : 120.
No. of patients in whome side effects were observed : 97.

Symptom	No. of Cases.
Tremors	32
Polyuria/Polydipsia	25
Memory defects	14
Excess salivation	12
G. I. disturbances	12
Weight gain	9
Hypothyroidism	7
Tardive dyskinesia	4
Acne	4
Fall of hair	4
Gait disturbance	1

Symptoms such as tremor, salivation and G. I. tract disturbances occurred early, within the first three months of initiation of therapy, whereas memory defects, weight gain, polyuria and gait disturbances appeared between 3 months to one year (Table II).

TABLE II—*Time of appearance of symptoms after initiation of therapy.*

Early (upto 3 months)	Intermediate. (3 months—1 year)	Late. (after 1 year).
Tremor	Memory defects.	Hypothyroidism.
Excess salivation.	Weight gain.	Tardive dyskinesia
G. I. disturbances	Polyuria.	Acne.
	Gait disturbance.	Fall of hiar.

Excess salivation, acne, gastro-intestinal disturbances and gait problems were transient and settled spontaneously. Memory deficit, viz., impairment of short term recall at 15-second interval, lasted longer but became less disturbing as days passed. These memory defects have been earlier reported by us (Sugumar et al., 1980).

Tremors : (N=32) : Fine tremor, usually of fingers was the commonest symptom, noted quite early during therapy. In seven patients the tremors were controlled with 40 mg propranolol per day which was discontinued after 2-3 months and tremors did not recur. In others, the magnitude of the tremors diminished over time and settled without any measure to counter. Two patients developed marked tremulous ataxia. Mrs. B. who was free from tremors during a continuous period of 2.5 years of therapy with lithium and subsequently during a seven month drug-free period experienced severe tremors within a week of restarting lithium; the serum lithium was 1.6 mMol/litre when she had severe tremors. The second patient, Mr. M., had tremors within four days of starting on lithium for the first time. This patient received amitryptiline in addition and the serum lithium was

0.9 mMol/litre. Lithium was withdrawn from both of them resulting in cessation of tremors. In the first patient lithium was restarted after tremors subsided and during the six months of treatment till date, tremors have not reappeared.

Polyuria : (N=25) : Polyuria (24 hours urine volume : 3.2-4 litres) was reported by 25 patients. Renal function was investigated in all the patients and did not reveal any gross impairment. The polyuria was reversible (Venkoba Rao et al, 1979). Renal biopsy done on 13 of these patients showed non-specific renal changes (Venkoba Rao et al, 1981).

Weight gain : (N=9) : Weight gain was noted in 9 patients, with an average of 4.5 kg. (3-7 kgs). The increase was gradual over a period of 2-3 months. After the initial increase, however, there was a plateau : Over the next few months they returned to the pretreatment level.

Hypothyroidism : (N=7) : Seven patients developed clinical features of hypothyroidism including goitre, skin changes and fall of hair, over a period of 1.5—2.5 years of therapy (Mean : 1.7 years). They were treated with thyroid; lithium was continued without any further impairment of thyroid function. Clinical features of hypothyroid state receded.

Relation to Serum levels and dosage of lithium : All the side effects were experienced while the oral dose of lithium was 750-1000 mg/day in 3 divided doses and the serum lithium levels well within the range of 0.6—1.2 mMol/litre. There was no correlation between these and any specific side effects.

Relation to Clinical Response : Out of the 120 patients, 43, who were continuously on lithium for 4 years or more, were chosen for examining side effects reported by them in relation to their clinical response. They were divided into two groups—Group I & Group II. Group I maintained remission without any relapse and Group II suffered relapses during therapy. Table III shows the observations.

TABLE III

	Group I	Group II
Total No. of patients:	13	30
No. in whom side effects were observed:	10(77%)	22(70%)
Neuromuscular (Tremor, Gait problems)	8(80%)	13(59%)
CNS (Memory defect, Tardive dyskinesia)	8(80%)	8(36.3%)
G. I. (Nausea, loose bowels, excess salivation)	9(90%)	8(36.3%)
Endocrine and Metabolic (Hypothyroidism, weight gain)	4(40%)	12(54.5%)
Water balance (Polyuria)	8(80%)	12(54.5%)

Of the 43 on long term therapy, 13 were good responders (Group I) with no relapses; of these 10 (77%) had side effects. Of the 30 moderate responders (Group II), 22 (70%) had side effects. The difference in incidence between the groups was not statistically significant. In the Group I the incidence of G. I. problems, tremors and polyuria was significantly higher than in the Group II. In the latter, however, endocrine and metabolic effects were more frequent (54.5%) than in Group I (40%).

DISCUSSION

The gastrointestinal problems of nausea, looseness of bowels and abdominal discomfort are said to occur in conjunction with the absorption of the ion and its rising blood concentrations. While mild hypermotility of the intestines, nausea and changes in appetite can occur even with low serum levels, frank diarrhoea and vomiting indicate imminent toxicity and call for stopping lithium (NIMH report

1970; Schou, 1976). The latter symptoms did not occur in the patients we studied.

Tremors and polyuria were the most frequent symptoms in the patients, as in certain other reports. A significant reduction in these symptoms following discontinuation of lithium has been suggested as evidence that they are genuine side effects due to lithium (Christodoulou and Lykouras, 1982). In our study too, the severe tremors experienced by two patients disappeared on withdrawal of lithium confirming the tremorigenic role of Lithium. Hand tremors during lithium therapy have a frequency different from Parkinsonian tremors and are believed to be non-extrapyramidal (Asnis et al., 1979). They are not relieved by anticholinergics but are amenable to beta-blockers (Schou, 1976). The present study confirmed this. Betablockers may be discontinued after reduction in tremors without recurrence of tremors in many. In intoxication, the fine tremors progress to coarse tremors and predispose to cogwheel rigidity (Schou et al., 1976; Asnis et al., 1979).

Tardive dyskinesia, noted in 4 cases of our series mitigated without any specific treatment. This is of interest in the context of reports that lithium might be of benefit in tardive dyskinesia (Reda et al., 1975). There are reports of extrapyramidal features during lithium therapy (Shopsin and Gershon, 1975; Branchey et al., 1976 and Asnis et al., 1979), and also on aggravation of pre-existing tardive dyskinesia by lithium with near toxic levels (Crews et al., 1977).

Memory defects, observed earlier in our study (Sugunner et al., 1980) and by others (Judd et al., 1979; Kusumo and Vaughan, 1977) are not severe and tend to clear over time. Others report no significant memory problems during lithium therapy (Telford and Worrall, 1978; Engelsmann, 1980; Singh et al., 1982).

Lithium induced hypothyroidism and goiter have been described by many investigators (Schou et al., 1976; Fieve and Platman, 1968, 1969). The reported incidence of hypothyroidism varies from 6-30% (Lindstedt et al., 1977). In this study it is about 9% ($N=7$) out of the 78 patients who were on treatment for more than 1.5 years (the mean time of onset of hypothyroidism being 1.7 years of therapy in the present study), lower than the higher incidence (30%) reported by Fieve and Platman (1968, 1969). In these studies, estimations of thyroid hormones in blood have enabled detection of latent hypothyroidism also. Our study has been limited to clinically manifest cases. The anti-thyroid effect of lithium is inherent in its anti manic effect. Lithium inhibits release of thyroxine and reduces the intra-thyroid indothyronine/iodotyrosine ratio (Sedvall et al, 1968). Latent hypothyroidism is believed to set in early as a natural physiological sequel, corrected by the pituitary thyroid axis (NIMH report, 1970). An increase in TRH and TSH occurs secondarily and restores the balance; A few cases of transient thyrotoxicosis consequent on increase in TRH and TSH have been reported as evidence of an overadaptive response to lithium. induced hypothyroidism (Reus et al., 1979; Brownlie et al., 1976; Rosser, 1976).

Weight gain has been reported to be a frequent effect of lithium treatment (Kerry et al., 1970; Grof et al., 1973; Vendsborg et al., 1976). In the present study, only 9 out of 120 (7.5%) have gained weight more than 3 kg between 3 months to 1 year of treatment. Changes in lipid metabolism, increase in serum megnesium and calcium and changes in carbohydrate metabolism with increased glucose tolerance (Mellerup et al., 1973; Vendsborg, 1979) have been suggested to be associated with weight increase. A metabolic readjustment is presumed to

occur, since after an initial increase, the gain reaches a plateau and slowly returns to the pre-treatment weight levels.

In the present study, there has been no occasion to study foetal anomalies due to lithium. The 42 females included unmarried girls, widows and divorced women who are not remarried, patients who have had tubectomy and post-menopausal women; others did not conceive during the period of lithium therapy.

RELATION TO DOSE AND SERUM LEVELS:

All the patients received regular preparations of lithium consuming the daily requirement in two or three divided doses. As such any specific advantage of single dose schedule over the divided dose regimen can not be made out from this study. Mellerup et al. (1979) observed that tremor, polyuria and weight gain are seen both in patients taking single daily doses as well as in those taking two or three doses. Except in two of the patients the side effects in the present study were not severe enough to warrant discontinuation of treatment. No specific relation has been detected between serum levels and side effects. In some reports tremor, nausea and abdominal discomfort were found to be related to the peak levels of serum lithium (Persson, 1977) whereas this was not found by others (Edstrom & Persson, 1977; Fyro et al., 1970).

RELATION TO CLINICAL RESPONSE

Ananth et al. (1977) observe that there is a greater incidence of side effects in the responders and that they tended to experience more endocrine side effects than the non-responders. Grof et al. (1973) report a positive association between weight gain and response to lithium. The findings of the present study on the other hand indicate a higher occurrence of neurological, gastro intestinal and renal side effects in the good responders and endocrine and metabolic effects (hypothyroidism, weight gain) in the moderate responders.

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