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Plasma Lithium Levels and Therapeutic Outcome in the Prophylaxis of Affective Disorders: A Retrospective Study

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Summary: Patients receiving prophylactic lithium therapy for primary affective disorder during a four year period were studied for recurrence of affective illness. Patients who had affective episodes during this period did not differ from those who remained well in age, sex or diagnosis. Those with a favourable outcome had spent significantly less time at serum lithium levels above 0.9 mmol/litre than those who had a recurrence of affective episodes.

The use of lithium salts in the treatment of manic illness and in the prevention of bipolar mood swings in manic depressive illness is firmly established (Prien, Caffey, and Klett, 1972a; Coppen *et al*, 1971). There is also some evidence that lithium is an effective prophylactic in unipolar depressive illness (Prien, Klett and Caffey, 1973). In the management of lithium therapy, the importance of using adequate doses of lithium to achieve optimum plasma levels is often stressed (Gershon, 1968; Schou *et al*, 1971). There is general agreement that lithium is most effective when serum levels measured 8 to 18 hours after the last dose of the drug are maintained between 0.7 to 1.2 mmol/litre (Schou, 1968; Prien and Caffey, 1976). Serum levels are thought to reflect the level of lithium in the brain tissue (Prien, Klett and Caffey, 1972b).

It has been suggested that our knowledge of serum lithium levels to produce therapeutic response is more fragmentary than is generally realized in everyday clinical practice or from the confident assertions found in some of the literature (Grof, 1979). So far only few attempts have been made to correlate serum levels with response. It has been accepted that the level necessary for effective prophylactic treatment is sometimes close to that effective in mania, although with other drugs such as anticonvulsants and antibiotics the prophylactic dose is considerably less than the curative dose. To study this relationship between plasma lithium levels and treatment outcome, we examined data from patients attending hospital for prophylactic lithium therapy between 1 January 1975 and 31 December 1978.

Patients and Methods

A cohort of patients was selected from those receiving prophylactic treatment with lithium at the Royal Edinburgh Hospital on 1 January, 1975. Selection was based on the following criteria:

(i) A definite diagnosis of primary affective disorder. Diagnostic criteria for Psychiatric Research (Feighner *et al*, 1972) were applied to relevant information from the case notes to arrive at this diagnosis.

(ii) Patients were free of affective symptoms at the start of the study on 1 January, 1975. They were not resident in hospital nor were they receiving concurrent psychoactive medication except for mild tranquillisers like benzodiazepines.

(iii) At the start of the study at least six months had elapsed after their last affective episode.

(iv) Patients were well stabilised on lithium therapy. This meant they had been on prophylactic lithium therapy continuously for a minimum of six months and were attending the out-patient clinic for regular serum lithium estimations.

Out of a total of 170 patients receiving prophylactic lithium therapy at that time 53 met the above criteria. They formed the subjects of the study and their case records were examined systematically. For each subject the following information was collected: age, sex, diagnosis of primary affective disorder (unipolar or bipolar), number and nature of previous affective episodes, length of time on lithium therapy and family history of psychiatric illness. In addition, results of all serum lithium estimations carried out during the trial period were obtained from a central lithium register. Dates of all estimations were noted. Therapeutic outcome during the trial was evaluated in terms of occurrences of affective episodes between 1 January, 1975 and 31 December, 1978. An affective episode was defined as a manic or a depressive episode requiring hospitalization or supplementary drugs or electroconvulsive therapy.

Statistical analysis

Since the aim of the study was to look at the relationship between outcome during prophylactic lithium therapy and steady state plasma lithium levels, subjects were divided into two groups depending on the outcome; those who had no affective episodes during the study period, and others who had one or more affective episodes during the same period. The significance of family history of psychiatric illness, previous episodes of affective illness (prior to commencing lithium therapy), subjects' age and length of time on prophylactic lithium were assessed in relation to outcome by analysis of variance and chi-square tests.

Since the main analysis of the study concerned the relationship between results of serum lithium estimations and therapeutic outcome, it was important to obtain a valid measure that reflected serum lithium levels over a period of four years. The estimations were spread over different time intervals and there were considerable variations within the same individual. The average value for such a variable would give a false impression. Hence, a linear interpolation method was used to arrive at a more valid measure of overall serum lithium level for each subject. Underlying this approach was the assumption that changes in serum lithium levels between two readings was in a linear fashion, and it was then possible to calculate the number of days each subject spent at various serum lithium levels.

The serum lithium range of 0 to 2.0 mmol/litre was divided into twenty groups, each with a range of 0.1 mmol/litre. The number of days each subject spent in the various groups was calculated. The total number of days was reckoned between the first and the last serum lithium estimation during the trial period. This was roughly 4 years for all subjects. The percentage of total time that each subject spent below any value from 0.1 mmol/litre to 2.0 mmol/litre was calculated. This was expressed as 'Percentage of time serum lithium below', or PLIB. For example, PLIB 4 was the percentage of time spent below a lithium of 0.4 mmol/litre. Analysis of variance of PLIB 1 to PLIB 20 with good and bad outcome was carried out. PLIB was used as the criterion variable.

Results

Subjects

There were 53 subjects (23 men, 30 women) who met the inclusion criteria, 41 bipolar and 12 unipolar. Their mean age on 1 January 1975 was 52.7 years (range 25–70 years). Three patients from the bipolar group developed their first manic illness during the trial period.

Of the total subjects 45 had had an episode of depression (85 per cent) before commencing prophylactic lithium therapy, and 38 had one or more episodes of mania. More than half the subjects had a history of psychiatric illness in their first degree relatives (28 out of 53). Seventeen had a definite family history of depressive illness while only four had a first degree relative with a manic illness.

All the subjects had started lithium treatment before 1974. There were four who had been on lithium for eight years by the beginning of the study, but the average time was 4.04 years. There was great variation in the number of lithium readings for each subject during the trial period: the average was 22.4 readings per subject (range 9–44).

Outcome

Twenty subjects (18 bipolar) developed affective episodes in the study period, and were compared to those who had remained without recurrence or relapse. Their mean age was 52.9 against 52.6 for those who remained well. In a two way analysis of variance with age as the criterion variable and bipolarity and occurrence of affective episodes as the interaction

TABLE I

Comparison of outcomes and family history of psychiatric illness

Outcome	No of subjects	F/H of any Psych. ill.	F/H of depression	F/H of mania
Good outcome group	33	18	13	3
Poor outcome group	20	10	4	1
Total	53	28	17	4

$\chi^2 = 0.00$; df = 1; nss.

$\chi^2 = 0.06$; df = 1; nss.

38 out of 53 subjects had episodes of mania before the trial period, but only 4 had a family history of mania. Three other subjects with no family history of mania had a manic episode for the first time during the trial period.

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variables no statistically significant difference was found (F = 0.3, df 1/49, ns). Nor was there any significant difference in length of time on lithium, nor did polarity affect outcome. (Poor outcome group contained 2 unipolars and 18 bipolars. on lithium for 3.9 years; good outcome group contained 10 unipolars and 23 bipolars, on lithium for 4.1 years). Table I shows that the poor outcome group did not differ significantly from the rest of the sample in terms of family history. Nor did the groups differ in terms of episodes of illness before lithium (good outcome 33 patients had 23 manic and 28 depressive episodes; poor outcome 20 patients with 15 and 17 episodes respectively).

Plasma lithium levels

For each subject, the percentage of time during the trial period spent below various serum lithium levels was calculated (PLIB). Analysis of variance of PLIB groups with the two outcomes was carried out (Table II). The good outcome group spent significantly more time at lithium levels below 0.9 mmol/litre. In other words, those who did not relapse during the trial period spent more time at what would normally be considered inadequate serum lithium levels. Examining percentage of time spent in the therapeutic range, i.e. between 0.8 and 1.2 mmol/litre, the same trend persists but does not reach statistical significance. The poor outcome group spent 60 per cent of the time in the therapeutic range and the good group 56 per cent (F = 0.247, df = 1/51 ns).

From the analysis of PLIB and outcome there was no consistent association between lower plasma levels and poorer outcome. In fact, the results suggested that those who developed affective episodes during the trial had spent less time with serum lithium levels below the lower end of the therapeutic range. Those who relapsed during the trial period might have had their serum lithium levels maintained at a higher level subsequently because of their high risk of relapse, but when the PLIB was recalculated using only serum lithium levels obtained up to the moment of relapse the result was much the same, and therefore this was not the explanation of the difference between the two groups.

Discussion

Historically, the appreciation of the clinical value of serum lithium levels has developed slowly. From monitoring safety it has progressed through monitoring adequacy of lithium treatment to the management of lithium poisoning (Grof, 1979). Evidence of a direct relationship between average serum lithium levels and therapeutic outcome is limited. There is some empirical evidence that within a range of 0.77 mmol/litre to 1.3 mmol/litre no relationship exists between average plasma levels in each patient and clinical response (Coppen *et al*, 1971).

The main conclusion of the present study must be that the relationship between serum levels of lithium and therapeutic outcome is not a simple one; maintaining patients within a therapeutic range (0.7–1.2 mmol/litre) is not always crucial to favourable response. This is in keeping with the results of a prospective dose-response study conducted by Jerram and McDonald (1978). They were trying to establish minimum effective serum levels in preventing relapse in a series of well-established lithium-responsive patients attending a lithium clinic. Their study demonstrated that long-term prophylactic treatment

TABLE II

Comparison of outcomes with times spent at various lithium levels

Serum lithium less than	PLIB—Means of percentages of time spent below given serum levels			F df = 1/51	P
	Entire sample	Poor outcome	Good outcome		
0.3 mmol/l	0.3	0.6	0.1	1.044	NS
0.4 mmol/l	0.9	1.7	0.4	1.9	NS
0.5 mmol/l	2.9	4.3	2.0	1.39	NS
0.6 mmol/l	6.6	7.8	6.0	0.32	NS
0.7 mmol/l	16.7	15.6	17.3	0.09	NS
0.8 mmol/l	37.9	33.7	40.5	0.92	NS
0.9 mmol/l	63.3	53.5	69.1	5.71	<0.05
1.0 mmol/l	80.1	71.4	85.4	7.24	<0.01
1.1 mmol/l	89.8	84.5	93.0	6.63	<0.05
1.2 mmol/l	95.5	93.3	96.8	3.57	NS
1.3 mmol/l	98.0	96.5	98.9	6.86	<0.05

PLIB has been calculated as the percentage of the total study period of four years on lithium. Recalculation using only the period from the start of the study to the relapse date of each patient makes little difference to the results.

could be satisfactorily maintained with serum levels as low as 0.4 mmol/litre. Our study has also failed to show that pre-lithium morbidity or history of psychiatric illness in the family affected outcome in a significant manner, although Mendlewicz *et al* (1973) had found that response to lithium was significantly related to the presence of bi-polar illness in the proband's first degree relatives.

Our finding that relapsing patients spent less time at low lithium levels than those who had remained well could perhaps be explained by supposing that clinicians had recognized a high risk group and prescribed a higher lithium dose in an attempt to prevent relapse. Alternatively side effects may equally well have discouraged both patients and clinicians from attempting to avoid relapse with continual high dosage.

Amdisen (1980) has recently questioned the usefulness of single plasma measurements guiding lithium therapy. However, these single measurements are what are routinely used for monitoring the patient and it is on their value in such monitoring that our results throw most doubt. However, it must be noted that all the subjects had responded favourably to maintenance treatment with lithium prior to the start of the trial period.

To test the hypothesis that patients with serum lithium levels within a given range will have a better outcome than those with levels outside that range requires a prospective dose-response study, with random assignment of similar patients to different doses of the drug with regular and frequent checks that the assigned level is being maintained and the follow-up double-blind. Until this is done we cannot be confident that lithium maintenance at a given level is necessary for effective prophylaxis.

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