EFFICACY OF LITHIUM PROPHYLAXIS IN BIPOLAR AFFECTIVE DISORDER

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Forty-four patients attending the affective disorder clinic at JIPMER Hospital who were on prophylactic lithium for bipolar affective disorder were studied. Intra-individual comparison for severity of illness was made between periods of similar duration with and without lithium prophylaxis. It was found that during lithium prophylaxis patients did significantly better on the following parameters: number of episodes of illness, duration of episodes, hospital admission, neuroleptic dosages and duration of antidepressant treatment. Of the 44 patients included in the study, 45% were good responders, 39% were partial responders and 16% were poor responders. Late age of onset was found to be a significant predictor of good response to lithium.

Key words: lithium prophylaxis, bipolar affective disorder, response.

INTRODUCTION

Initial reports (Cade, 1949; Schou et al., 1954) showing usefulness of lithium salts in treating affective disorders were followed by research showing the prophylactic action of lithium (Hartigan, 1963; Baasstrup & Schou, 1967). The longitudinal study by Angst et al. (1970) using the mirror image design first brought lithium to the attention of the international psychiatric community. Subsequently, several prospective studies including random assignment, double blind and placebo control studies have generally supported the usefulness of lithium as a prophylactic agent in bipolar disorder.

Dunner and Fieve (1974, 1976) have struck a discordant note showing an early rapid failure during the first six months of treatment, questioning the conventional wisdom of using lithium. Response to lithium prophylaxis also varies enormously across different studies. Baasstrup and Schou (1967) showed that 86 out of 88 patients with Manic Depressive Psychosis (MDP) responded well to lithium prophylaxis, whereas, Aagard and Vestergard (1990) found that the overall response was poor with 40% of their patients experiencing two or more readmissions during a two year follow-up.

In the Indian context, the efficacy of lithium in the prophylaxis of affective disorders have been studied with wide ranging results. Venkoba Rao and Subramaniyam (1978) reported a 41.7% response over a five to eighteen month follow up period. Narayanan et al. (1979) reported an almost universal good response in a group of twenty three patients followed up for a period ranging from eighteen to twenty three months.

At JIPMER, the lithium clinic is run as a part of the affective disorder clinic and patients are regularly followed up once in two weeks. The present study was undertaken in our clinic to take a fresh look regarding the usefulness of lithium prophylaxis and identify predictors of response.

AIMS

1. To find out whether lithium prophylaxis significantly improves the course of bipolar affective disorder.
2. To find out the proportion of patients who benefit from lithium.
3. To identify the characteristic of responders.

MATERIALS AND METHODS

At the outpatient service of psychiatry department, JIPMER, new cases are worked up by residents and a diagnosis is made in conference with a consultant psychiatrist in accordance with the existing version of the International Classification of Diseases. During follow up at the affective disorder clinic, the decision to start lithium on a prophylactic basis is also made by consultants. Lithium carbonate is administered as 150 or 300 mg. tablets and the dosage is adjusted to maintain a serum lithium level of 0.6 to 0.8 meq/liter. Serum lithium levels are routinely assessed, initially once a week until dosage adjustment is done and once in three months subsequently.

In the present study, the case records of all patients with a diagnosis of Manic Depressive Psychosis (Manic type) i.e., 296.1, MDP circular 296.3 (according to ICD 9), attending the follow up clinic were scrutinized.
Cases were included if they satisfied the following conditions:

1. If they suffer from recurrent episode of illness.
2. Had at least two affective episodes in two years prior to lithium administration.
3. Taken lithium for a period of at least 18 to 24 months and should be preceded by a similar duration without lithium.

Those cases with serum lithium levels below 0.6 meq/l, irregularity in intake of lithium and lack of contiguous period (with and without lithium) were excluded. A detailed case chart review was undertaken to obtain socio-demographic, illness and treatment details. The number of episodes of mania and depression, number of symptomatic days, number of hospital days, duration of hospitalization, the total dose of neuroleptics converted to chlorpromazine equivalents (Davis & Cole, 1975) and duration of antidepressants in weeks were recorded.

An episode was defined as any disturbance which was sufficiently symptomatic to require ECT or increased dosage of neuroleptics, antidepressants, lithium or required hospitalization (Modified Baastrup and Schou criteria). The episode during which the patient was started on lithium was taken to calculate the length of therapy, but excluded in statistics to avoid bias. If a manic episode was immediately followed by depressive episode then it was considered to be a single episode (Baastrup & Schou, 1969).

Patients were assigned to three outcome groups depending upon whether their response to lithium was good, partial or poor (modified from Page et al, 1987).

1. **Good response**: there were no episodes of mania or depression requiring treatment while on lithium.
2. **Partial response**: episodes of illness occurred while the patients were on lithium but they were less often and less severe in terms of indicators of severity.
3. **Poor response**: there was no detectible change in frequency or severity of relapse after lithium prophylaxis was started.

Statistical analysis was done using the Statistical Package for Social Sciences. Paired t test, Wilcoxon's matched pair signed rank sum test and logistic regression analysis were used in the study.

**RESULTS**

The mean age of the study group was 33.15 years (SD ± 9.5) and 23 were males and 21 were females. The index episode was mania in 31 patients and depression in 13 patients. There was a positive fami-

| Indicators of Severity | Before Li (Mean) | During Li (Mean) | z/t Stat | p* value |
|------------------------|------------------|------------------|----------|-----------|
| Episodes               | 1.72 ± 0.29      | 0.83 ± 0.11      | z= 1.98  | 0.047     |
| Symptomatic days       | 68.50 ± 15.20    | 25.62 ± 29.29    | t= 1.63  | 0.001     |
| Hospital admission     | 0.36 ± 0.40      | 0.13 ± 0.30      | z= 2.84  | 0.001     |
| Hospital stay          | 9.10 ± 11.30     | 2.80 ± 7.00      | z= 2.90  | 0.005     |
| Neuroleptic dose (CPZ equivalence) | 466.25 ± 181.65 | 202.00 ± 85.00  | t= 9.62  | 0.001     |

**Table 2**

| Dependent/year | Independent B | b | t | p* value |
|----------------|--------------|---|---|----------|
| Episodes       | Lithium      | -0.75 | -0.54 | -6.23 | 0.001 |
| Symptomatic    | -0.59 | -6.62 | 0.001 |
| duration of illness | Lithium | -11.35 | -0.59 | -6.62 | 0.001 |
| Duration of illness | 0.41 | 0.24 | 2.18 | 0.03 |
| Hospital admission | Lithium | -0.06 | -0.31 | -3.05 | 0.003 |
| Hospital stay | Lithium      | -1.57 | -0.31 | -3.03 | 0.003 |
| Neuroleptic dose | Lithium | -66.11 | -0.68 | -8.75 | 0.001 |
| Duration of antidepressant | Lithium | -1.65 | -0.21 | -2.06 | 0.04 |

**Table 3**

Logistic predictor analysis for response to lithium

| Variables | B | Significant | R |
|-----------|---|-------------|---|
| Age of onset | 0.2437 | 0.02* | 5.42486 |
| Family history | 0.9860 | 0.34 | 0.00000 |
| Age | 0.0396 | 0.73 | 0.00000 |
| Sex | 0.3377 | 0.76 | 0.00000 |
| Rapid cycleto | 0.4220 | 0.63 | 0.00000 |

*p < 0.05, Independent significant effect
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ly history of affective disorder in first degree relatives in 20 patients. The mean serum lithium of the study group was 0.71 meq/l (SD ± 0.17).

Comparison of pre-lithium and lithium periods on various parameters related to severity of illness are shown in Table 1. A significant reduction was noted on all the indicators of severity of illness. A step wise multiple linear regression analysis confirmed that the relationship between severity of illness and lithium carbonate cannot be explained by variations in other variables and that the association between lithium and severity of illness is a real one (Table 2). Categorization of 44 patients on the basis of number of episodes showed that the 20 were good responders (45%), 17 were partial responders (39%) and 7 were poor responders (16%). Logistic predictor analysis was done to identify the predictors of response to lithium and the age of onset was found to be the sole predictor.

DISCUSSION

In the present study design intra-individual comparison of severity of illness for two contiguous periods of equal duration of illness (one without lithium and the other with lithium) were made. If lithium has no prophylactic action, the course of illness as judged by the indicators of severity should remain unchanged both before and during treatment. As is evident from Table 1 there was a significant difference between the pre-lithium and lithium periods on every one of the indicators. Similar findings have been reported in previous studies (Baastrup & Schou, 1967; Angst et al, 1970; Page et al, 1987). A multiple linear regression analysis was performed and this confirmed the prophylactic action of lithium. The proportion of good responders (45%), partial responders (39%) and poor responders (16%) in the study is similar to the figure obtained by Aagard and Vestergard (1990). In various studies the proportion of responders vary from 30% to 90%. This may be explained partly on the basis of variation in diagnostic criteria, patient selection, duration of follow up etc.

In this study an attempt was made to find out the predictors of response to lithium. The only predictor of response was age of onset, i.e, later the age of onset, the better the prognosis. This findings is an agreement with Aagard and Vestergard (1990). Taylor and Abrams (1975) reported younger age of onset as a predictor of good response. Angst et al (1970) and Prien et al (1974) did not find any correlation between rapid cycling (patients with four or more affective episodes per year) and lithium prophylaxis. Rapid cycling patients with four or more affective episodes per year) did not come out as predictors as observed in other studies (Dunner & Fieve, 1976; Page et al, 1987). Prien et al (1974) had shown that rapid cyclers respond poorly to lithium prophylaxis. Taylor and Abrams (1975) and Aagard and Vestergard (1990) have shown poor response among female patients as compared to male patients. This study did not identify female sex as a significant variable.

The problems faced in this design include (a) compliance was not ensured (b) there could have been an over representation of good responders in a follow up clinic, and (c) clustering of episodes in pre-lithium period. Oral compliance was partially taken care of by estimation of serum lithium levels. The latter two problems can only be overcome in a prospective design by minimizing attrition and by excluding the period prior to lithium prophylaxis.

To conclude, lithium prophylaxis is not 100% effective. Relapses do occur during treatment by they are less in number and severity than before the introduction of lithium treatment. Later age of onset predicts good response to lithium. The authors are of the view that factors influencing response to lithium remain to be classified in Indian patients using a prospective design.

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