VALPROATE IN ACUTE MANIA
- A CONTROLLED STUDY

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ABSTRACT

A controlled blind study was carried out to establish the efficacy of Sodium Valproate as the first line of treatment in Acute Mania. Patients were studied over a period of 4 weeks. Using randomised table patients were assigned to either lithium or valproate. Decrease in the psychopathology was evident within 2-3 weeks. Valproate was found to be as effective as Lithium in controlling the manic episode.

Key Words: Acute mania, sodium valproate, drug treatment

Acute mania is associated with substantial negative personal, interpersonal and social consequences. Effective and rapid pharmacological control of the condition is a necessity and towards this a variety of agents are available currently. They are lithium, antipsychotics, benzodiazepines, anticonvulsants like carbamazepine, valproate etc. Review of literature by Licht (1998) recently reveals that there is diversity in the preference of agents as the first line of treatment in acute mania across countries. Lithium continues to be used extensively both in USA and Europe. Valproate is the recommended agent in the North American continent in the recent times (Joffe, 1993; APA, 1994; Bowden, 1996). Antipsychotics as the first line of treatment are losing ground in the West although it is still used as an adjunct especially in cases with psychotic symptoms (Soares et al., 1997). In India, in clinical practice antipsychotics and lithium continue to be the preferred drugs in acute mania. Published data from India on the efficacy of anticonvulsant like valproate in acute mania is not available. Hence the present study was undertaken to validate the effectiveness of sodium valproate in comparison to lithium in the treatment of acute mania in the Indian population.

MATERIAL AND METHOD

The study was conducted at the Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore. Consenting patients with an ICD-10 diagnosis of mania or bipolar affective disorder (BPAD) currently manic were taken for the study. Written informed consent was obtained from the patients and a near relative. Due to practical reasons the study sample consisted of only male patients. The diagnosis was confirmed by two clinicians independently after a detailed psychiatric evaluation. All the patients in the study were admitted during the period of the trial - 4 weeks. Patients were in the age group of 16-45 years. Patients were either drug naive or had stopped medication one month before the current consultation. Patients with comorbid illness like epilepsy, substance abuse, personality disorders etc. were excluded from the study. Detailed physical examination was done. Laboratory test (complete haemogram, liver function tests, renal function tests & thyroid function tests) were done.

Patients were randomly assigned to two
groups - first group received lithium carbonate and second group received sodium valproate. Each patient had an equal chance of being included in either group I or II. The first author (HMP) who was blind to the medication received by the patients serially rated patients. Beigel's Mania Rating Scale (BMRS) - a scale with proven reliability and validity was used for rating the severity of the psychopathology (Beigel, 1971). It has 26 items to rate both the intensity and the frequency of the manic signs. The scale covers behavioural and cognitive symptoms of mania. This scale has been used in similar studies (Leher et al., 1987). Rating was done on the 1st, 3rd, 7th, 14th, 21st and 28th day of the admission.

Total number of patients recruited for the study was 26. However, 5 patients withdrew their consent before four weeks. These included 3 in lithium group and 2 in valproate group. Patients who withdrew the consent had either improved partially or significantly (n=2) or did not want to continue inpatient care for personal reasons (n=2); one patient developed hepatitis and hence was dropped from the study (drug valproate). The final sample consisted of 21 patients. Group I had 11 patients whereas group II had 10.

Patients in group I received lithium carbonate (available as 300 mg tablet each) in the range of 900-1500 mg. Serum lithium level was measured on the fifth day after starting the drug. Based on the serum lithium levels, the dosage was adjusted by the treating clinician not involved in the study. At the end of four weeks serum lithium levels ranged from 0.6 to 1.1 mEq/L in the group (mean=0.84 mEq/L±0.18 mEq/L). Patients in group II received sodium valproate (available as 200 mg tablet each). The loading dose of valproate was 20 mg/Kg. It was increased up to 1400 mg if needed by the clinician depending on the clinical improvement. Dosage in the group ranged from 600 to 1400 mg. Monitoring of the serum levels of valproate though planned was not feasible due to the high costs involved. The total dosage of either lithium or valproate was given in three divided doses every day. The rater (HMP) was blind to the treatment received by patients. Any side effects reported was recorded but no structured instrument was used to assess the side effects.

Patients with severe excitement received benzodiazepines for the first few days. Antipsychotics were not used during the study period at any time.

This study was not supported by any pharmaceutical company.

RESULTS

Paired 't-test' was used to compare continuous variables and 'chi square' was used to compare discrete variables between the two groups. The dropouts were not included in the analyses.

The two groups of men did not differ in terms of age, weight, and the duration of the current episode of mania [(p=0.159, 0.495, 0.718 respectively) (table)].

### TABLE

| Variable                  | Lithium (n=11)* | Valproate (n=10)* |
|---------------------------|-----------------|-------------------|
| Age in years              | 23.73           | 25.70             |
| Weight in kg              | 48.45           | 52.40             |
| Duration of current episode (in weeks) | 5.60 | 6.10 |
| Dose mg/day               | 1145.45         | 1240.00           |
| BMRS score on 1st day     | 307.73          | 290.10            |
| BMRS score on 28th day    | 97.64           | 63.00             |
| Total benzodiazepam received in mg | 39.09 | 28.89 |

*mean values

An improvement of more than 50% on BMRS was considered as good response. The total score on the BMRS on first day was compared with the scores on 3rd, 7th, 14th, 21st and 28th day and a reduction of more than 50% in the total scores by the 28th day was considered as a good response. 8 of 11 in the lithium group (72.72%) and 8 of 10 (80%) in the valproate group had good response. This was not statistically different (p=0.695). Most of the reduction in the total mean scores occurred in the second and third week in both the groups. There was no statistical difference between the two groups on the BMRS total mean scores on the 1st day (p=0.431), 3rd day (p=0.837), 7th day (p=0.459),
14th day (p=0.297), 21st day (p=0.803) and on the 28th day (p=0.315). There was also no significant difference in the change in the scores between the two groups on the individual items of the rating scale. However, there was trend for better reduction of total mean scores on 28th day in the valproate group (fig.). There was no difference in dosage of benzodiazepines received by either group (p=0.476).

**DISCUSSION**

In this controlled blind study, sodium valproate was found to be as effective an antimanic drug as lithium carbonate in acute mania. Out of 10 patients 80% responded to 600 to 1200 mg of sodium valproate within two to three weeks indicated by a 50% reduction in total scores in BMRS. Sodium valproate was comparable to lithium in the proportion of the sample that responded and the time frame over which they responded. Other randomised controlled studies of valproate and lithium though methodologically different have also concluded that valproate is comparable to lithium in its efficacy as an antimanic agent in acute mania (Bowden et al., 1994; Freeman et al., 1992, McElroy et al., 1991).

The percentage of good response to valproate was higher in this study in comparison to other studies - 80% vs 48% reported by Bowden et al. (1994) and 53% reported by McElroy et al. (1991) and 64% by Freeman et al. (1992). Preselection of the sample of acute mania with no mixed features or comorbidity is probably one of the reasons for this better outcome in the current study. However, it is to be remembered that Bowden et al. (1994) revealed through a post-hoc analysis of their data that the response to valproate was unaffected by the presence of depressive symptoms.

None of the recruited patients in this study were earlier established as poor responders to treatment either with lithium or antipsychotics. Inclusion of a sample (not by design) with no definite treatment resistance is probably the other reason for a better response to sodium valproate in this study in comparison to the other above mentioned studies.

Acceptance as far as side-effects were concerned was similar to lithium though hepatitis was encountered in one patient even in this small sample of ten. This study inspite of its stringent inclusion and exclusion criteria and methodology sample size is a limitation. The small sample size reduces the power of equivalence inspite of comparable outcome. Studies have pointed out that the better acceptability of valproate over lithium is due to its better side effect profile (Bowden, 1996). In this study both the drugs were well tolerated by the patients who completed the study, but it might be more accurate if a structured scale is used to record the side effects.

Although this study confirms the efficacy of sodium valproate in the treatment of acute mania in an Indian setup, it is essential and desirable to have more open studies with a better methodology with larger sample sizes and subtypes of mania to gain more experience.

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