RESPONSE OF CARBAMAZEPINE IN BIPOLAR DISORDER: KINDLERS VERSUS NON-KINDLERS

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ABSTRACT

Based on carbamazepine's hypothesized ability to stabilize temporal lobe seizures and behavioral disorders and its ability to inhibit limbic system excitability in models such as kindling, we undertook this study with the aims of finding out the response of carbamazepine in kindler and non-kindler groups and to see the relationship of socio-demographic and clinical variables in kindler and non-kindler bipolar mood disorder with response to carbamazepine. Simple random sampling was done and patients (over a period of one and a half year) between 18-50 years who had a diagnosis of Bipolar Affective Disorder, current episode mania as per ICD -10 and who had history of at least three manic or depressive episode in the past were taken. The total sample was divided into two groups i.e. kindler and non-kindlers. Kindlers were defined as patients with 3 or more affective episodes in less than equal to 1 year apart. Non-kindlers were defined as patients with at least 3 episodes in the past with inter episodic period of more than 1 year. All the patients included in this study were followed up for 6 months and were given carbamazepine in adequate dosages. Fifty-five patients completed the 6 months follow up. Results showed that there was no significant difference between the two groups based on sex, past history of substance intake, type of mood (irritable versus elated), number of relapses during the follow-up and improvement on carbamazepine. Our study does not support the kindling hypothesis.

Key Words- Carbamazepine, kindlers, non-kindlers.

Neuropsychiatric theories about bipolar disorders have emphasized models of kindled limbic system activity as a possible mechanism to explain recurrent phases of illness. In this paradigm, it is hypothesized that regular, frequent period of early affective illness may trigger more subsequent episodes via an excitatory mechanism analogous to that seen in seizure disorders (Post et al., 1986; Post and Weiss, 1992).

According to Post's theory (Post et al. 1986. Post, 1992), affective symptoms both within and between episodes are thought to have a kindling or sensitization effect with progressively lower thresholds for new episodes. As advanced by Post (Post & Weiss, 1989), this theory builds on the physiological finding that intermittent sub threshold electrical or chemical stimuli produce increasing strong neuronal depolarization of the brain, a process of sensitization that may possess temporal similarities to the episodic behavior disturbances of bipolar disorder.

Several studies have described a shortening of cycle lengths over the course of the illness (Cutter & Post 1985; Roy Byrne et al., 1985; Kessing et al. 1998).

Several such studies involving patients with bipolar disorder were consistent with kindling
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(Ambelas 1979; Dunner et al., 1977; Goldberg and Harrow 1994; Gitlin et al 1995; Kessing et al 1998), whereas others did not support (Turvey et al 1998), or were indeterminate (Winokur et al 1993).

But, the studies supporting the kindling hypothesis are not so strong from methodological point of view.

First the initial episode of mania is difficult to reliably locate in time, particularly in retrospective studies relying on patients' recollection (Ambelas 1979). Second, assessment of life events vary from study to study, ranging from standardized interview to clinical observation, to chart review (Kessing et al. 1998) and again often are limited by over reliance of patient’s self-report. Thirdly, life events may be cause or consequence of bipolar disorder and if studies would find as many or even more life events in later as in earlier episodes, it does not support the kindling hypothesis and also hospitalization data are the basis for a number of studies; the methodology captures severe but not the mild episodes which may make the result relevant for severe but not mild form of bipolar illness.

The newest data derived from a well designed prospective study of course of bipolar disorder as a part of the NIMH collaboration study of depression (Turvey et al., 1998) in which 165 patients with type I bipolar disorder or schizoaffective disorder mainly affective type were followed prospectively for about 7 years, reveal no evidence of a shortening of cycle length with time. Instead poor prognosis was associated with polyphasic (change of polarity in the same episode) episodes Roy Byrne et al. (1985) and Maj et al. (1995) also reported association between switching and higher relapse rates. These findings suggest that polyphasic episodes are a common clinical presentation of poor prognosis in bipolar I disorder.

Dunner et al.(1974) first coined the term rapid cycling in a land mark paper that summarized longitudinal data designed to evaluate clinical factors associated with the failure of lithium prophylaxis. When the study results were analyzed according to cycle frequency, a disproportionate percentage of rapid cyclers were noted in the lithium failure group (82% rapid cyclers failure compared to 41% failures in the classic group).

Numerous studies have proven the efficacy of carbamazepine in bipolar mood disorders, especially so in rapid cyclers (Post et al., 1983), either as a single drug or in combination with lithium or neuroleptics

Post et al. (1987) studied 19 acutely manic patients in a double blind trial of carbamazepine in doses averaging 1240 mg per day. The blood level of carbamazepine was 10.4± 2.2 μg/ml. The preliminary data suggested that several predictors of poor response to lithium (manic severity, dysphoria, rapid cycling and negative family history) might be associated with good antimanic response to carbamazepine.

Placidi et al. (1986) studied the comparative efficacy of carbamazepine versus lithium in 83 bipolar patients and followed for 3 years. The respective indices of relapse per group did not differ significantly. It was concluded that lithium salt might be more efficacious in ‘classical’ affective disorder (i.e. major recurrent depression, bipolar disorder with mood congruent features) whereas carbamazepine is more effective in the treatment of other group (bipolar psychosis with mood incongruent features, schizoaffective disorder or schizophreniform disorder).

Greil et al (1998) in a randomized, prospective, multicenter study (N= 67) with an observation period of 2.5 years reached similar conclusions.

Based an carbamazepine’s hypothesized ability to stabilize temporal lobe seizures and behavioral disorders and its ability to inhibit limbic system excitability in models such as kindling, along with the above mentioned controversial literature, we undertook this study with the aims of finding out socio-demographic and clinical characteristic of patients with kindler and non kindler mood disorder, to see the response of carbamazepine in kindler and non kindler groups and to see the relationship of socio-demographic...
and clinical variables in kindler and non-kindler bipolar mood disorder with response to carbamazepine.

MATERIAL AND METHODS

The study was conducted at the Central Institute of Psychiatry, Kanke, Ranchi (643 bedded hospital, about 150,000 outpatients and 1800 admissions per year)

The present study had a prospective design. Simple random sampling was done and patients (over a period of one and a half year) between 18-50 years who had a diagnosis of bipolar affective disorder, current episode mania, with or without psychotic features as per ICD -10 (WHO 1992) and who had history of at least 3 manic or depressive episode in the past were taken.

Putative kindling was operationally defined for patients with three or more preindex episodes less than or equal to one year apart. Kindlers were compared to bipolars with preindex episodes greater than one year apart (Goldberg and Harrow, 1994).

Exclusion Criteria were any other axis I and axis II diagnosis, and clinical evidence of organic, substance induced disorder, neurological disorder and mental retardation.

Within 48 hours of the admission, the patient and key relatives were interviewed on socio-demographic and clinical data sheet to gather information.

All the patients included in this study were evaluated on Brief Psychiatric Rating Scale (BPRS) to capture the type of psychopathology that is affected by drug treatment, Young’s Mania Rating Scale (YMRS) to assess the resolution of symptoms of mania, and Hamilton Depression Rating Scale (HDRS) to assess the development of depressive episode during the treatment period at 0 hours (Within 48 hours of admission), 2 and 4 weeks during admission and also at 3 months and 6 months during follow up after discharge.

All the patient included in this study were given carbamazepine in adequate dosages. Exact dosing of carbamazepine and other drugs like anti-psychotics and hypnotics was left to the treating team.

Chi-square test was employed for analysing categorical data, while t test and paired t test were used for analysis of continuous data.

RESULTS

Initially 66 patients were taken for the study. Out of this 55 patients completed the 6 months follow up and rest 11 patient did not come for follow up after being discharged from the hospital. The drop out at 3 months was same as that at 6 months i.e. 11 patients.

| Variable                  | Group          | t value |
|---------------------------|---------------|---------|
| Age                       | 32.10±9.75    | 35.57±8.86 | t=1.48 |
| Number of past episodes   | 7.47±3.52     | 4.78±3.48  | t=3.03*|
| Dose of CBZ               | 718±108.69    | 728±124.29 | t=0.35 |
| Duration of illness       | 43.21±58.69   | 48±35.43   | t=1.68 |

The dose of carbamazepine was 718 mg (± 108.69) for kindler group and 728 mg (± 124.29) for non-kindler group. No significant difference was found between the two groups in doses(Table I).

In the sample, the number of past episodes was 7.47 (± 3.62) in kindler group and 4.78 (± 3.48) among non-kindler group and significant difference (p < .05) was found between the two groups(Table I). There was no significant difference in age and duration of illness amongst the two groups.

There were 84% males and 15% females in the kindler group and 85% males and 14% females in the non-kindler group(Table II).

Results show that both groups were simi­lar in respect to marital status, occupation, domi-
cile, past history of psychiatric illness, type of medication used (antipsychotics and benzodi­azepines), relapse to mania / depression, history of substance use and type of mood (Table II).

TABLE 2
SOCIO-DEMOGRAPHIC AND CLINICAL PROFILES OF KINDLER AND NON-KINDLER GROUPS (FOR CATEGORICAL DATA)

| Variable          | Kindler | Non kindler | Chi Square |
|-------------------|---------|-------------|------------|
| Sex               | n (%)   | n (%)       |            |
| Male              | 32 (64.2) | 24 (85.7)  | 0.01       |
| Female            | 6 (15.8)   | 4 (14.3)   |            |
| Marital           | 28 (73.7) | 24 (85.7)  | 0.77       |
| Married           | 10 (26.3)   | 4 (14.3)   |            |
| Occupation        |         |            |            |
| House wife        | 7 (18.4)  | 3 (10.7)    | 0.86       |
| Student           | 4 (10.5)   | 3 (10.7)    |            |
| Residence         |         |            |            |
| Rural             | 25 (65.8) | 18 (64.3)  | 0.01       |
| Urban             | 13 (34.2) | 10 (35.7)  |            |
| Past history      |         |            |            |
| Mania             | 24 (63.2) | 17 (60.7)  | 0.01       |
| Mania + depression| 14 (38.8) | 11 (39.3)  |            |
| Family history    |         |            |            |
| Absent            | 19 (50)  | 15 (53.6)  | 0.01       |
| Present           | 19 (50)  | 13 (46.4)  |            |
| Type of Medication|        |            |            |
| CCBZ +            | 11 (28.9) | 9 (32.1)   |            |
| Benzodiazepine    |         |            |            |
| CCBZ + Antipsychotic| 27 (71.1) | 19 (67.9) | 0.01       |
| Relapse to mania  | 4 (13.3)  | 1 (4)       | 2.72       |
| Relapse to depression | 1 (3.3) | 3 (12) |            |
| Substance history |         |            |            |
| Absent            | 25 (65.8) | 21 (75)    | 0.28       |
| Present           | 13 (34.2) | 7 (25)     |            |
| Mood              | 37 (97.4) | 24 (85.7)  | 1.68       |
| Elation           | 1 (2.6)  | 4 (14.3)   |            |
| Irritable         |         |            |            |

For all comparisons d.f.=1 except occupation where it is 3
All values of χ² were not significant

The history of substance intake in the form of cannabis and alcohol abuse was found in 34.2% of kindler patients and 25% in non-kindler patients with no statistically significant difference (Table II).

TABLE 3
COMPARISON OF TREATMENT RESPONSE DURING FOLLOW-UPS FOR KINDLER AND NON KINDLER PATIENT ON BPRS SCORE

| Variable          | Kindler | Non Kindler |
|-------------------|---------|-------------|
|                  | (N=30)  | (N=25)      |
| Mean ± SD        | t       | Mean±SD     | t          |
| BPRS at 1st contact | 14.23±5.82 | 9.56* 14.68±5.26 | 9.71*       |
| BPRS at 2nd week  | 6.2±5.03  | 7.2±5.31    |            |
| BPRS total at 1st contact | 14.23±5.82 | 10.05 14.68±5.26 | 12.90*     |
| BPRS at 1 month  | 3.29±4.23 | 3.8±5.73    |            |
| BPRS at 3-month  | 0.66±2.07 | 0.8±2.02    |            |
| BPRS total at 1st contact | 14.23±5.82 | 10.60 14.68±5.26 | 11.17*     |
| BPRS at 6 month  | 1.13±2.94 | .7±2.15     |            |

* p<0.01

TABLE 4
COMPARISON OF TREATMENT RESPONSE DURING FOLLOW-UPS FOR KINDLER AND NON KINDLER PATIENT ON YMRS SCORE

| Variable          | Kindler | Non Kindler |
|-------------------|---------|-------------|
|                  | (N=30)  | (N=25)      |
| Mean ± SD        | t       | Mean±SD     | t          |
| YMRS at 1st contact | 24.3±6.49 | 15.52 22.24±6.01 | 12.80*     |
| YMRS at 2nd week  | 7.8±5.53  | 7.0±5.23    |            |
| YMRS total at 1st contact | 24.2±6.12 | 15.90 32.2±6.01 | 12.12*     |
| YMRS at 1 month  | 6.2±4.55  | 6.4±6.25    |            |
| YMRS total at 1st contact | 24.3±6.99 | 17.23 22.2±6.01 | 12.40*     |
| YMRS at 6 month  | 3.2±4.9  | 1.8±1.91    |            |

* p<0.01
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During six months follow up, four patients (13.3%) relapsed into mania in the kindler group and one patient (4%) relapsed into mania among the non-kindler group. No significant difference between the two groups in terms of relapse was found (Table II).

Comparing the total score on BPRS, statistically significant reduction of total score was found on successive follow-ups with maximum reduction in scores at 3 months in both the kindler and non-kindler groups (Table III).

Similarly on YMRS scale significant reduction of total score was found on successive follow-ups with maximum reduction in scores at 3 months in both the kindler and non-kindler groups (Table IV).

DISCUSSION

In the earlier studies the dose of carbamazepine was higher in bipolar patients (Post et al., 1983; Placidi et al., 1986) than that used in our study but this difference might be due to different pharmacodynamics and pharmacokinetics of the drugs in Indian population. We found in our study that the number of past episodes in the kindler group was significantly greater (p<.05) than the non-kindler group which does not support the previous results by Goldberg and Harrow (1994) who did not find any significant difference of number of past episodes among kindler and non-kindlers. But this is in congruence with other previous studies (Cutler & Post 1985; Roy Byrne et al., 1985; Kessing et al. 1998), which suggested shortening of cycle lengths over the course of illness.

We found no statistically significant difference in the number of males and females in the two groups (kindlers vs. non-kindlers). This finding is different from previous studies (Bauer et al., 1994; Dunner et al. 1977) where a significantly higher proportion of females were found in rapid cycler group. The lesser number of female patients can be attributed to the social bias against seeking psychiatric consultation for the female gender in our country. The male is more likely to be the wage earner and thus gets immediate attention when his wage earning capacity is affected (Khanna et al., 1992).

Our study supports the common co-morbidity of substance abuse in affective disorder patient though there is no significant difference amongst the two groups in this aspect.

Our finding of no significant difference between the two groups in terms of relapse does not corroborate with Goldberg & Harrow (1994), where kindlers had a significantly higher number of relapses as compared to non-kindlers on 2 years and 4.5 years follow-up.

One reason could be comparatively shorter follow up period in current study. None of the patient in Goldberg and Harrow’s study was on anti epileptic mood stabilizer while in current study all patient were on anti epileptic mood stabilizer, which is of proven efficacy in preventing the relapse in kindlers (Post et al. 1992). Furthermore, their sample size (N=26) was small in comparison to the current study.

Our results of maximum improvement within three months of treatment support the previous findings by Placidi et al. (1986) who studied 83 bipolar patient on double blind trial of carbamazepine and lithium and followed up for three years and found that patient showed maximum improvement within first three months of treatment and then maintained this improvement up to 12 months of follow up.

The phenomenon of three patients changing their polarity also supports the previous findings. Tohen et al. (1990) followed up seventy-five bipolar manic patients for four years. Eleven subjects (15%) cycled into depression during the index hospitalization within the first two months period. As the total population was high (N=66) and total score of HDRS was less, mean and standard deviation were negligible and because of this it could not be discussed.

Our study does not support the kindling hypothesis. The reason behind that may be follow up in our study was less in comparison to previous studies (Kessing et al. 1998; Goldberg & Harrow, 1994). Secondly, patients in previous studies got
anti depressants during treatment, which is a known cause of switching.

Keeping in mind some of the limitations of the present study, a few recommendations for future research are in order. Though the sample size taken was modest, a larger number of patients would give greater significant results. The patients should be followed up for long periods of time that will give more clear picture of effect of drugs. More female patients should be included in the study and if both the groups would get only carbamazepine in adequate dosages it would give more accurate results. Side effect of drugs should have been rated. Thyroid status of the patients should have been checked biochemically which was not done in this study as thyroid abnormalities may contribute to rapid cycling. Type of antipsychotics and hypnotics used, and their doses should have been controlled for, which was not done in the current study.

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