THE USE OF CARBAMAZEPINE IN PATIENTS WITH MANIC DEPRESSIVE ILLNESS

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SUMMARY

16 cases of affective disorder were studied. 8 patients received carbamazepine and 8 received either chlorpromazine or imipramine. Ratings were carried out on the Hamilton Rating Scale for Depression, Bech Rafaelsen Mania Rating scale and a side-effects symptom check list. Carbamazepine was found to be an effective treatment for affective disorders, possessing both anti-manic as well as anti-depressant properties.

The fact that carbamazepine is an iminodibenzyl derivative and an established antiepileptic agent, may be useful in psychiatric disorders was noted many years ago (Marjerrison et al., 1968). Most of the early reports were of uncontrolled clinical trials. The psychotropic effects of carbamazepine have, since, been studied extensively (Pryse-Phillips & Jeavens, 1970; Rodin et al., 1974). Dalby (1975) in a review of 40 reports found that 50% of 2500 patients with epilepsy improved psychiatically when given carbamazepine. The phasic disorders of epilepsy resembling functional psychiatric syndromes, especially manic-depressive illness and schizophreniform psychoses, often show a dramatic response to carbamazepine. Sometimes this response is without a concomitant reduction in the frequency of seizures (Dalby, 1975). Recent investigations, therefore, have been directed towards delineation of the possible role of carbamazepine in the management of affective disorders. Investigators, mainly from Japan and the U. S. A. have suggested that carbamazepine may be effective in manic depressive illness (Folks et al., 1982; Ballenger & Post, 1980; Okuma et al., 1979; and Takezaki & Hanaoka, 1971). Okuma and associates (1979) compared the anti-manic efficacy of carbamazepine and chlorpromazine. They reported an overall improvement of the patients on Carbamazepine to be about 70%.

Recent reports have also shown that carbamazepine may be effective in affective disorders in a synergistic fashion with lithium. Forrest (1982), in a case report, described the case of a 45 years old man with Right Hemispherectomy (done for intractable epilepsy) who developed a rapid cycling bipolar illness. This responded well only when carbamazepine was added to lithium. A similar report of synergism between carbamazepine and lithium has been described by Lipinski et al (1982).

Ballenger and Post (1976, 1978) have postulated a kindling model of affective psychoses, wherein cumulative bioelectrical changes, particularly in the limbic area, secondary to repeated biochemical or psychological stresses, could result in abnormal limbic neuronal sensitization and major psychiatric disturbances. Carbamazepine has been demonstrated to suppress after discharges (Koella et al., 1975) and spontaneous and induced seizure discharges preferentially in limbic areas over other cortical areas.
(Dementrescu & Julian, 1974). The neurophysiologic actions of carbamazepine could be efficacious in treating the “kindled” affective disorders as postulated by Ballenger and Post (1980).

Further, a recent review of world literature suggests that from 30-40% of patients treated prophylactically with lithium do not respond (Barney, 1982). Therefore, it is essential to develop alternatives to lithium carbonate. Carbamazepine would seem to fill this need. However, presently there is an urgent need to evaluate carbamazepine in a larger population of patients to find out as to which patients respond to carbamazepine (CBZ) and whether it is effective in patients who do not respond to lithium. Its synergistic and efficacious combination with lithium also needs to be looked into. Hence, keeping in view the abscence of any Indian report on this topic, we decided to carry out a pilot investigation into the role of carbamazepine in Manic-Depressive Illness.

MATERIAL AND METHODS

An open study on the effects of Carbamazepine was planned. Patients diagnosed as either Major Depressive Disorder or Bipolar Disorder according to DSM-III were included into the study. Patients with depression were then started on either Imipramine (IMI) or Carbamazepine (CBZ) according to a randomization schedule. Similarly, manic patients were started randomly either on chlorpromazine (CPZ) or CBZ. The affective states were monitored throughout the study period for days 0, 3, 14, 21 and 28 of four weeks. Patients on IMI were given 75 mg. IMI per day for 3 days, which was then increased to 150 mg. for 14 days. If at the end of day 14 there was less than 70% improvement on the Hamilton Rating Scale for Depression, then the dose was increased to 200 mg/day.

Patients on CPZ were given 600 mg. of CPZ for 3 days which was then increased to 1000 mg. till day 14. If there was less than 70% improvement on the Bech-Rafaelsen Mania Rating Scale then the dose was increased to 1300 mg/day. All patients on CBZ were given 600 mg. of CBZ for 3 days. Dose was then increased to 1000 mg/day till day 14. If there was less than 70% improvement then the dose was increased to 1600 mg/day. The ratings were carried out on the following instruments: (i) The Bech-Rafaelsen Mania Rating Scale, (ii) Hamilton Rating Scale for Depression, (iii) Side-effect symptom Check-list, (iv) Clinical Global Impression Scale. All patients were between 18 and 55 years of age. Pregnancy and evidence of any major physical illness were exclusion criteria. All patients were given thorough clinical physical examination and were investigated, including complete blood count, platelet count and ECG.

OBSERVATIONS AND RESULTS

This is a report of 16 cases, of which 8 were on Carbamazepine and 8 on chlorpromazine or Imipramine (depending upon the clinical state). Of the 8 patients on CBZ, 6 showed moderate to marked improvement in their clinical status. One patient (B. L.) showed only about 30% improvement while another showed marked side effects of CBZ which resulted in a discontinuation of her trial. This young female (37 yrs. old) was diagnosed as case of recurrent bipolar affective disorder, being in the depressed phase at the start of trial. She was without any side effects till day 5, i.e., one day after increase of dose from 600 mg. to 1000 mg. From day 5 she developed nausea, dizziness and vomiting. On days 6 and 7 she was given lower dose (600 mg/day) of CBZ but there was no resolution in these side effects. Patient was, therefore, found
Table 1. Patient characteristics and response to CBZ Treatment

| Sl.No. | Age  | Sex  | Diagnosis         | Dose After Day 14 (per day) | PT. Response to Carbamazepine |
|--------|------|------|-------------------|----------------------------|--------------------------------|
| 1.     | 37   | F    | Dep. Bipolar      | Discontd. after day 8 when patient was on 1000 mg/day of CBZ. She developed marked dizziness, nausea, vomiting, loose motions and finally dehydration. Resolved after CBZ discontinued. | Marked improvement in Mania apparent on day 14. Side effects mild and transient. Almost completely recovered by day 28. |
| 2.     | 38   | M    | Mania Bipolar     | 1000 mg.                   | Moderate improvement. 75% reduction in symptoms by day 28. S/E mild+Transient. |
| 3.     | 44   | M    | Bipolar Mania     | 1000 mg.                   | Moderate improvement. Only 50% (approx.) reduction in symptoms by day 28. Developed diplopia on day 5. transient. |
| 4.     | 48   | M    | Major Depr. Disorder. | 1600 mg.                   | Moderate improvement. 80% reduction by day 28. Nausea, dizziness and blurred Vision. Transient. |
| 5.     | 52   | M    | Depression Bipolar. | 1000 mg.                   | Marked improvement, Transient ataxia on day 7 for 1 day. |
| 6.     | 45   | M    | Major Depr.       | 1000 mg.                   | Ditto—Transient ataxia, clumsiness and blurred Vision. |
| 7.     | 45   | M    | Bip. Mania        | 1000 mg.                   | Moderate improvement. Only about 70% reduction in symptoms by day 28. Ataxia & Drowsiness transiently on the latter 2 occasions of increase in dose. Shurred speech. Nausea also. |
| 8.     | 40   | M    | Major Depr.       | 1600 mg.                   | Moderate improvement. |

quite dehydrated on day 8, when it was decided that the drug had to be discontinued and patient was managed on I. V. fluids for her immediate problems. Scores on HRSD by end of wk. 1 had not shown any significant alteration. Ratings on the B-R Mania Rating Scale and HRS for Depression showed that the maximum improvement occurred by day 14 of the study period. A similar assessment of patients on either CPZ or IMI shows that of the 8 patients who completed the clinical trial, only 2 showed mild to moderate improvement. One of these 2 was a patient of major Depressive disorder, 39 yrs. old, who manifested only less than 50% improvement on 200 mg/day of IMI. This patient was also quite troubled by mainly dizziness and postural hypotension. Physical examination and laboratory investigations did not reveal any physical abnormality. None of the patients on any modality of treatment showed any hematologic or cardiac abnormalities during the trial period. The major side effects observed with CPZ or IMI were not of such an intensity so as to warrant a discontinuation in any patient. Amongst the side effects of Carbamazepine-dizzi-
TABLE 2. Patient Characteristics and Response CPZ/IMI Treatment

| Sl. No. | Age | Sex | Diagnosis      | Medication and Dose after day 14 (per day) | PT. Response to Medication         |
|--------|-----|-----|----------------|-------------------------------------------|-----------------------------------|
| 1.     | 32  | M   | Bipolar Mania  | COZ 1300 mg.                              | Marked improvement. EPS present throughout. |
| 2.     | 35  | M   | Bipolar Mania  | CPZ 1300 mg.                              | Moderate improvement. 80% reduction by day 28. EPS and postural hypotension transient. |
| 3.     | 39  | M   | Bipolar Mania  | CPZ 10000 mg.                             | Marked improvement. Minimal side effects. |
| 4.     | 47  | F   | Bipolar Depression | IMI 150 mg.            | Moderate-Marked (85%) improvement by day 28. Postural hypotension transiently. |
| 5.     | 29  | M   | Bipolar Mania  | CPZ 1000 mg.                              | Moderate-Marked (75%) improvement by day 28. |
| 6.     | 34  | M   | Bipolar Mania  | CPZ 1300 mg.                              | Only 60% reduction by day 28. Frequent concomitant need for sedation. Side Effects minimal. |
| 7.     | 44  | M   | Major Depression | IMI 200 mg.            | Marked improvement by day 28. Postural hypotension transiently in 3rd week. |
| 8.     | 39  | M   | Major Depression | IMI 200mg.                 | Less than 50% improvement by day 28. Side effects (postural hypotension, dizziness), quite prominent. No cardiac abnormalities on ECG. |

TABLE 3. Side effects of carbamazepine in 8 Patients of M. D. Illness

| Symptom       | No. of Patients |
|---------------|-----------------|
| 1. Dizziness  | 6               |
| 2. Nausea     | 6               |
| 3. Ataxia     | 3               |
| 4. Diplopia   | 2               |
| 5. Blurred Vision | 3             |
| 6. Drowsiness | 1               |
| 7. Clumsiness | 1               |
| 8. Slurred Speech | 1          |
| 9. Vomiting   | 1               |

Dizziness and nausea were the ones most commonly observed. Usual time of onset of side-effects was from day 4 onwards and usually disappeared on the same dose after a gap of about 2-5 days. 3 Patients also developed mild ataxia and tremors which were transient. 2 patients complained of blurred vision and on examination also had definite diplopia. This side-effect was also transient in both subjects. Drowsiness, slurred speech, clumsiness and vomiting were noted in 1 patient each. None of the patients developed any skin rash, cognitive impairment, confusion, weakness and aching in legs, paraesthesia or cardiac arrhythmias (being the other commonly reported side-effects of CBZ). One patient
developed a doubtful postural hypoten­sion, noted only on one occasion at night by the resident on emergency duty. Subsequent monitoring next morning or thereafter did not reveal any such finding. In the night there was a systolic difference of 24 mm. of Hg and a diastolic difference of 10 mm. of Hg. No patient on CPZ manifested any extrapyramidal side effects and drowsiness/sedation was uncommon. Rarely, patients on CBZ were needed to be given concomitant medication, the side effects being managed usually on the same dose or a slight transient reduction of the same. Most patients on CPZ needed antiparkinsonian medication. In this study 'marked' improvement was usually attributed to patients manifesting over 90% reduction in ratings on the scales, irrespective of the side-effects. A patient manifesting over 70% improvement was considered as 'moderately' improved.

DISCUSSION

This report is the first from our country regarding the efficacy of Carbamazepine in Affective Disorders. This is an ongoing study and an initial, pilot investigation at our centre where in we are comparing the efficacy of CBZ with established psychotropic agents (CPZ & IMI) in an open study design. The initial impression given by this trial indicates CBZ to be at least as effective as IMI/CPZ in Depression/Mania. Prophylactic effects were not studied in this trial. Side effects were not found to be limiting except in one out of 8 patients.

Carbamazepine has a ring-like structure similar to that of imipramine and it has been in use since the late 1950s as the principal treatment for trigeminal neuralgia and since 1962 for psychomotor epilepsy. Its side effects which are most frequently reported rarely necessitate discontinuation of treatment (Parsonage, 1975). Side effects are reported to be minimized if the increase in dosage is slow/gradual and the serum levels remain below 12.0 µg/ml. This observation is quite consistent with our own observations where in we usually noted transient side effects to appear from day 4 onwards: our study design having determined that after day 3 the dose of CBZ was to be increased from 600 mg/day to 1000 mg/day stabilization at the higher dose, and therefore an expected stabilization of serum levels were enough to dispense with the side-effects. Ballenger and Post (1980) reported that their patients improved on CBZ usually by the 1st week of treatment and the antimanic effects continued throughout the 3 wk trial. We have a similar experience, when we notice that our patients usually improved by day 14 to quite an extent and only 2 patients required the dose of CBZ to be increased from 1000 to 1600 mg/day. Improvement, once occurred, continued to be manifest throughout the study period. Folks et al. (1982) reported that CBZ may have antimanic as well as anti-depressant properties. Our study, although open in nature, also seems to suggest a similar finding. The other conclusions drawn by these authors viz., (a) CBZ may be effective in some lithium non-responders (b) CBZ and Li or CBZ and antidepressants may have synergistic efficacy and that (c) CBZ may be especially useful in CNS disordered patients with affective syndromes, could not obviously be tested owing to the study design employed in our study. Doubtless, these observations are important areas for future investigation. Moreover, it would be surely desirable to assess the prophylactic efficacy of CBZ in recurrent affective disorders. Reports suggesting the importance of CBZ in rapid cyclers need to be substantiated too. We have already planned a crossover study using CBZ and Lithium. CBZ, with its antimanic properties may
be a useful antidepressant in the fact that it would be free to the problem of induction of mania in bipolar depressed patients, a hazard reported with other antidepressant medication (Wehr & Goodwin, 1979). Thus, finally, we feel that well-controlled studies are surely needed in this area and these would throw additional light into the management and aetiological understanding of Affective disorders.

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