POTENTIATION OF LITHIUM WITH CARBAMAZEPINE IN ACUTE MANIA

B. N. GANGADHAR
NIMESH G. DESAI
S. M. CHANNABASAVANNA

SUMMARY

In a 6 month prospective randomized open trial addition of 400 mgs. of carbamazepine per day to lithium carbonate was assessed. Although statistically non-significant, the trends suggest that use of carbamazepine hastens recovery and leads to less frequent use of emergency sedation without any increase in side effects.

While lithium carbonate has been found to be the most effective drug in treatment of acute mania, other drugs like sodium valporate, verapamil and carbamazepine are also in use. Of these drugs carbamazepine has been of intensive research focus as a therapeutic and prophylactic agent for affective disorders. Combining carbamazepine and lithium carbonate is proved to be effective in refractory or treatment resistant mania (Desai et al. 1983, Keishing, 1983, Elphick 1985) suggesting a favourable therapeutic interaction between these two drugs. The possibility of using such an interaction in routine treatment of mania has not so far been considered. Hence, we attempted to compare lithium alone and lithium with fixed dose of carbamazepine in acute mania with respect to the clinical efficacy, side effects and the need for emergency sedation.

Material and Methods

Over a six months period patients with a diagnosis of mania were considered for this study with the following criteria.

Inclusion - (1) Diagnosis of Manic Episode as per DSM-III (APA 1980). (2) Age between 18 and 45 years.

Exclusion - (1) Past history of non-response to lithium (2) Current episode already on treatment (3) Patients on lithium or any other psychotropic medication in last 6 months (4) Contraindication for lithium or carbamazepine therapy, including renal function tests.

All patients were hospitalised after obtaining consent from a relative for the proposed trial. These patients were randomly allocated to receive carbamazepine 200 mgs, twice daily with lithium carbonate (Li+CBZ group) or lithium carbonate (Li alone group). For all patients lithium carbonate was stepped up from an initial dose of 900 mgs. per day to higher doses to reach therapeutic range of 0.8 to 1.2 mEq/L in serum within first 10 days. At the end of the 4 week trial period carbamazepine was discontinued. Lithium carbonate was continued for patients of both the groups for six months unless there was an indication for prophylaxis in which case the duration was longer than 6 months.

The clinical state was rated on the Bech Rafaelsen Mania Scale (BRMS) (Bech et al. 1979) pre-treatment and at weekly intervals by two raters and their rating scores were averaged for each occasion. An overall clinical global rating of mania was done on a 0-15 scale. A check list consisting of equal number of common side effects described

1. Department of Psychiatry, NIMHANS, Bangalore.
for lithium and carbamazepine was used for weekly ratings. Intravenous injections of 10 mgs. of haloperidol were permitted to be used for emergency sedation in the ward as per the decision of the ward resident.

Results

Ten patients, five in each group (seven females, three males, age range 19-43 years) were included for the trial after screening 24 patients. The patients in the two groups did not differ with respect to relevant clinical variable including the pre-treatment (Wk 0) BRMS scores.

As is evident in the figure there was a trend towards a larger fall in BRMS scores in the Li + CBZ group. A 50% reduction in the original score occurred within one week in the Li + CBZ group while the same required two weeks in the Li alone group. All patients of the combination group reached a score of zero at the end of 4 weeks whereas in the Li alone group only two patients reached a score of zero at 4 weeks and one patient did not show any response at all. This patient responded in the next two weeks with addition of carbamazepine. Global rating of mania also show similar trends.

The mean values of BRMS scores at pre-trial or Wk 0 rating did not differ significantly between the two groups (t = 1.19 NS) suggesting that the two groups of patients were comparable in the severity of mania. Inter group comparison of the mean BRMS scores on test did not reveal significant differences on any of the later occasions.

Intra group comparison of the mean BRMS scores at each of the later occasions (Wk 1 to Wk 4) with the pre-trial (Wk 0) mean BRMS scores showed a significant reduction of symptoms in both the groups on all occasions. This period effect observed in both the group proves that significant improvement occurred during each of the four weeks with lithium-carbamazepine combination as well as lithium alone. The higher values seen for the combination group suggests that the improvement occurred at a faster rate in the combination group.

Table shows: two patients in the Li + CBZ combination group reported one side effect each during the trial whereas three patients in the control group reported two symptoms each. This indicates that addition of carbamazepine to lithium does not lead to increased side effects.

The number of injections used for emergency sedation with haloperidol also differed in the two groups. The patients in the combination group required two injections in the first week and none in the next three weeks. The group of patients who received lithium alone needed twelve injections in the first week, six in the second week and one each in the third and fourth weeks.

Discussion

The trends observed in this study support earlier views (Nolen 1983, Lipinsky & Pope 1982) of a possible synergistic action of lithium carbonate and carbamazepine in mania. We have explored the possibility of achieving an advantage by combining a fixed dose of carbamazepine (400 mgs. per day) to lithium carbonate. The higher number of emergency injections of haloperi-
Table

| BRMS Score (Mean ± S. D) | Li + CBZ Group (N = 5) | Li alone Group (N = 5) |
|--------------------------|------------------------|------------------------|
| Wk 0                     | Wk 1                   | Wk 2                   | Wk 3       | Wk 4       | Wk 0       | Wk 1                   | Wk 2                   | Wk 3       | Wk 4       |
| 22.6 ± 4.3               | 10.6 ± 3.8             | 5.2 ± 2.6              | 1.6 ± 0.8  | 0          | 26         | 15.8 ± 2.0            | 12.4 ± 3.4            | 8.8 ± 3.9  | 8.6 ± 4.5  |
| 14.34                    | 9.63                   | 9.68                   | 4.00       |             | < 0.01     | 2.70                   | 2.99                   | 3.25       | 3.06       |
| Y Value with Wk 0 (Compared to baseline Mean) | < 0.01 | < 0.01 | < 0.01 | < 0.1 | < 0.05 | < 0.05 | < 0.05 | < 0.05 |

ridol in the lithium alone group is likely to have lowered the BRMS scores, thus narrowing the differences between the groups. The non-responder in lithium alone group showing good response after addition of carbamazepine further substantiates our earlier finding of the efficacy of carbamazepine lithium combination for lithium resistant mania (Desai et al. 1986).

Besides the small sample size and poor control over other emergency medication, the open design of this study prevent us from drawing any definite conclusions of the suggestive trends of faster improvement with the combination. The raters' bias in such a design may have worked either way and hence we have undertaken a double-blind placebo controlled study on similar lines.

The finding of potentiating action of carbamazepine on lithium in acute mania, if confirmed in later studies, is likely to be useful in routine clinical practice by reducing the period of incapacitation or hospitalization. This is all the more so since there seems to be no increase in the side effects. The issues of the period for which such a combination should be used and whether carbamazepine should be used in a fixed dose regimen or more flexibly are certainly open to debate.

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