CARBAMAZEPINE LITHIUM COMBINATION FOR LIPTHIUM RESISTANT MANIA

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SUMMARY

In an open prospective trial five cases of mania identified as lithium non-responders were treated with lithium – carbamazepine combination. The prophylactic efficacy of this combination was also studied. The combination proved to be therapeutically and prophylactically effective without significant side effects. The findings and relevant clinical issues are discussed.

Lithium carbonate is the most commonly used drug in treatment of mania. Although it’s therapeutic and prophylactic efficacy has been proved, the fact that a sizeable number of patients do not respond to lithium has necessitated the search for an adjunct or alternative in treatment of mania. Intolerable side effects or neurotoxicity observed with lithium, especially in combination with neuroleptics, are other reasons for an effort to look for therapeutic and/or prophylactic efficacy of other drugs in mania Flupenthixol, Sodium Valporate and its derivative depamide, Verapramil and Carbamazepine being the best established (Nolen 1983).

Carbamazepine (CBZ) has been studied as a single drug and in combination with lithium. Following their reports in the early 1970s of the antimanic effects of carbamazepine, Okuma et al (1979) demonstrated in a multicentred double blind study that carbamazepine was as effective as chlorpromazine in treatment of mania. Ballerger and Post (1980) showed carbamazepine to be an effective antimanic agent. Lipinsky and Pope (1982), Keishing (1983) and Desai et al (1983) identified manics in whom lithium or carbamazepine alone were therapeutically ineffective but in whom the combination of two drugs proved to be therapeutically successful. Use of carbamazepine for prophylaxis in manic-depressive illness or bipolar disorders has been demonstrated as a single drug (Folks et al. 1982) and in combination with lithium, neuroleptics or antidepressants (Kishimoto et al. 1983). The role of carbamazepine administered alone or in combination with lithium or neuroleptics in the therapy and/or prophylaxis of lithium-resistant bipolar illness has been further studied and confirmed (Post et al. 1984, Nolen 1983, Fawcett and Kravitz 1985, Elphick 1985).

Material and Methods

A nine month open, prospective study was conducted on all patients receiving an ICD – 9 diagnosis of manic depressive psychosis, mania (ICD codes 296.0 and 296.2). These patients were treated with lithium carbonate and neuroleptics and screened for nonresponse which was defined as “insignificant or no change in the clinical status despite maintaining a serum lithium level of 1.2 to 1.5 meq/L for a period of three weeks”. In such cases, carbamazepine in a dose of 400 to 600 mgs/day was added to the therapeutic regime and neuroleptics were gradually withdrawn. Recovery was
defined as the absence of manic or hypomanic symptoms on clinical examination. The patients have been followed up for observing the prophylactic efficacy of lithium-carbamazepine combination.

**Results**

Of 30 patients screened, 5 (17%) were identified as non-responders for the current episode. There were 4 females and 1 male, with ages ranging from 18-26 years. All but one patient had experienced several previous episodes of mania which had been resistant to lithium thus needing adjunctive high-dose neuroleptics, ECT and reserpine leading to severe extrapyramidal reaction in one and neurotoxicity in two.

In the current manic episode, once carbamazepine was started improvement was obtained in all five patients within just 2 weeks and was complete over the succeeding 2 weeks. Very few side effects like transient giddiness, drowsiness and/or nausea were noticed.

The other two patients (III and IV) were maintained on lithium alone for prophylaxis one patient (V) was lost to followup spanning 10 to 24 months. The two patients who did not respond to therapy with lithium in acute mania have also maintained improvement on lithium prophylaxis.

**Discussion**

This report describes patients who did not respond to lithium for therapy of acute mania being successfully treated with addition of carbamazepine. The need for using neuroleptics in high doses, in addition to lithium noticed in earlier episodes leading to severe side effects, was also avoided. The lithium–carbamazepine effect was found to initiate in 2 weeks' time with complete recovery in 4 weeks. There are reports of distressing and potentially serious side effects of carbamazepine alone or in combination with lithium (Choudhary and Waters 1983, Shukla et al 1984, Khaitan et al 1985, Elphick 1985). We did not find significant side effects supporting the view of Okuma et al (1979), Ballenger and Post (1980) and Nolen (1983) that carbamazepine is a safe drug in mania.

The followup findings suggest that lithium carbamazepine combination is also useful in patients who do not respond to prophylactic lithium. Two cases of therapeutic non-response to lithium showing good response to lithium prophylaxis.
make an interesting observation and raise important treatment issues. It is possible that therapeutic non-responders to lithium may be prophylactic responders to lithium? Can the patients who may require lithium – carbamazepine combination for treatment of acute mania be maintained on lithium alone for prophylaxis? Our finding suggests an answer in affirmative.

Certain lacunae exist in literature in general and in our study as well which merit attention in future studies. Lithium non-response both therapeutic and prophylactic needs to be better defined in terms of the time set and possibly with erythrocyte/serum lithium ratio instead of serum lithium as an index. Therapeutic and prophylactic efficacy needs to be assessed more objectively using appropriate rating scales rather than on clinical grounds. Serum levels of carbamazepine or its most active metabolite carbamazepine – 10, 11 Epoxide (CBZ-E) require investigation as suggested by Post et al (1984). Carbamazepine needs to be studied individually in comparison to lithium and the combination for therapy and prophylaxis.

These limitations notwithstanding, our open trial suggests a definite role for lithium – carbamazepine in lithium non-responders for therapy and prophylaxis in mania.

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