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EDITORIAL

Use of the anticonvulsant carbamazepine in primary and secondary affective illness: clinical and theoretical implications[1]

Carbamazepine is a tricyclic compound bearing some resemblance to imipramine, with an interesting spectrum of clinical efficacy in paroxysmal pain syndromes, paroxysmal neural discharges of seizure disorders, and in disorders of mood and behaviour. Although still somewhat controversial, increasing evidence is emerging that carbamazepine is efficacious in the treatment of mood and behavioural disturbances associated with psychomotor seizures or complex partial seizures (Dalby, 1971, 1975). Dalby's observations in 1971 and in his review in 1975 indicate that, in both open and controlled clinical trials, there is evidence of the psychotropic effect of carbamazepine which, in some instances, appears to occur independently of improvement in the underlying seizure disorder itself. While some investigators have argued that the positive psychotropic effects are either related to better seizure control or to the substitution of carbamazepine for other anticonvulsants, these do not appear to be sufficient explanations. In controlled clinical studies, positive effects on mood and behaviour are noted in both patient (Dodrill & Troupin, 1977) and normal volunteer populations (Thompson *et al.* 1980). Thompson, for example, noted significant and dose-related impairment of cognitive functioning in volunteers treated with phenytoin, but non-significant effects during carbamazepine administration. Moreover, the patients on carbamazepine reported themselves as more active, less tired, and less depressed, in contrast to those on phenytoin who reported themselves as more depressed, less active, and significantly more fatigued (Thompson *et al.* 1980).

Carbamazepine is a drug of choice in the treatment of complex partial seizures and other seizure disorders thought to be related in part to temporal lobe and limbic mechanisms. In parallel, there is clear-cut laboratory evidence that carbamazepine is more effective in suppressing seizures derived from temporal lobe and limbic sites than those from other neocortical areas. Albright & Burnham, for example, reported that carbamazepine was the most effective anticonvulsant in suppressing after discharges associated with amygdala compared with neocortical kindling (Albright & Burnham, 1980). Thus, carbamazepine has an interesting clinical and laboratory profile of relatively greater efficacy in suppressing limbic compared with cortical excitability. It is also effective in suppressing the progressive development of seizures, such as those manifest in kindling (Babington & Horovitz, 1973; Wada, 1977; Wada *et al.* 1976).

Two groups of Japanese investigators had reported in open clinical trials that carbamazepine was also useful in the treatment of patients with manic-depressive illness not associated with seizure disorder (Takezaki & Hanaoka, 1971; Okuma *et al.* 1973). In the light of these observations and the reports of carbamazepine's efficacy in affective illness occurring in association with epilepsy (Dalby, 1971, 1975) as well as its ability to suppress limbic system excitability and to inhibit amygdala kindling (Albright & Burnham, 1980; Babington & Horovitz, 1971; Wada, 1977; Wada *et al.* 1976), we were encouraged to proceed with the first controlled clinical trials of carbamazepine in patients with manic and depressive illness (Post *et al.* 1978, 1982*a*, *b*; Ballenger & Post, 1978, 1980).

Using a double-blind placebo-controlled design, we noted substantial antimanic efficacy when carbamazepine was substituted for placebo. Relapses occurred following placebo substitution, and patients again improved when carbamazepine was reinitiated. Patients were treated with an average dose of approximately 1000 mg/day, with blood levels between 6 and 12 ug/ml (Post *et al.* 1978, 1982*a*, *b*; Ballenger & Post, 1978, 1980). Okuma and associates (1979) have compared carbamazepine with chlorpromazine in the treatment of acute manic patients, using a double-blind methodology.

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They found that 70% of patients showed marked to moderate improvement with carbamazepine compared with 60% of those treated with chlorpromazine. The incidence of side-effects, particularly drowsiness, was significantly lower during carbamazepine than with chlorpromazine treatment. We and Okuma have not observed Parkinsonian side-effects occurring during the course of carbamazepine treatment, although occasional dystonias or dyskinesias have been reported in the neurological literature. Tardive dyskinesia has not been reported as a side-effect of carbamazepine treatment in epileptic patients, many of whom have been maintained on the drug for long periods of time. Moreover, unlike traditional neuroleptics, carbamazepine does not acutely block cocaine (Post *et al.* 1982*b*) or amphetamine-induced (Koella *et al.* 1975) hyperactivity and does not produce HVA elevations in the CSF of our psychiatric patients (Post *et al.* 1982*b*). Thus, it is likely that the mechanisms underlying the antimanic effects of carbamazepine are different from those of traditional neuroleptics and are not the result of direct dopamine receptor blockade. If this finding is confirmed, it would appear to be of theoretical interest as well as of clinical importance.

In our first 25 depressed patients, both bipolar and unipolar, we observed a 48% incidence of good to moderate antidepressant responses (Post *et al.* 1982*a*, *b*). In those patients who showed initial improvement, mild relapses were often observed following placebo substitution, while depression was not exacerbated in those patients who did not initially improve. These data further suggest that the improvement in depression was carbamazepine-related and that drug discontinuation was not associated with a non-specific withdrawal syndrome, but rather with some exacerbation of original symptomatology. In contrast to the rapid onset of antimanic effects and improvement in sleep disturbance noted in both manic and depressed patients within the first week, antidepressant responses did not generally occur until the beginning of the third week of treatment (Post *et al.* 1982*b*).

We have also observed substantial prophylactic responses to carbamazepine in 6 of 7 patients who were previously non-responsive to treatment with lithium carbonate (Post *et al.* 1982*b*). Improvement was particularly notable in 2 patients with severe and fulminant rapidly cycling manic-depressive illness who had required essentially continuous state hospitalization for several decades prior to admission to NIMH. These data suggest the potential usefulness of carbamazepine for treatment-resistant and rapidly cycling patients. Our findings parallel the early observations of Okuma and associates (1973) of a prophylactic effect of carbamazepine in 74% of patients suffering from manic episodes and 52% of patients with depressive episodes. A more recent clinical trial (Okuma *et al.* 1981) in 12 manic-depressive patients, using a double-blind methodology, indicated an effective rate for one year of carbamazepine prophylaxis at 60%, compared with only 22·2% in the placebo group ($P < 0{\cdot}10$).

We have observed positive responses to carbamazepine in patients with a classical presentation of manic or depressive symptoms, as well as in several patients with schizo-affective illness (Post *et al.* 1982*b*). One patient with a recurrent confusional psychosis also showed a positive response to carbamazepine. Recently, in an open study, Folks *et al.* (1982) reported improvement in 8 of 10 patients with bipolar ($N = 4$), schizo-affective ($N = 3$) and affective syndromes associated with evidence of a CNS disorder ($N = 3$). Stevens *et al.* (1979) reported exacerbation of psychotic symptomatology when carbamazepine was added to high-dose neuroleptic treatment in schizophrenics. However, we have not observed this in our patients with affective or schizo-affective illness, some of whom show further improvement when neuroleptics are added to carbamazepine (Ballenger & Post, 1978; Post *et al.* 1982*b*).

Thus, the early evidence is highly suggestive that carbamazepine may prove useful both in the treatment of a subgroup of patients with classical primary affective illness, as well as in a subgroup of patients with schizo-affective or more atypical presentations. Further studies are required to delineate clinical and biological markers of response to carbamazepine and to study whether these patients overlap with or represent a separate subgroup of patients responsive to routine psychotropic medications such as lithium carbonate, tricyclic antidepressants or neuroleptics. Further studies of carbamazepine would also appear indicated because of its different profile of side-effects compared with routine psychotropic drugs. As noted above, it does not appear to possess the liabilities of

neuroleptics in producing either a Parkinsonian or tardive dyskinesia syndrome or of exacerbating depressive phases of the illness, as has been reported for the antipsychotic agents (Kukopulos *et al.* 1980). Similarly, it would not appear to possess the liability of routine tricyclic antidepressants to increase the incidence of exacerbating manic episodes. In addition, in contrast to lithium carbonate, carbamazepine not only does not induce the diabetes insipidus (DI) syndrome, but it has been utilized to treat it (Wales, 1975; Maffy, 1977; Stevens *et al.* 1978). Early observations do not support the view that carbamazepine will reverse lithium-induced DI when the two drugs are used concomitantly (Ghose, 1978), but substitution of carbamazepine for lithium may alleviate the problems of DI. Recent data from our laboratory suggest that carbamazepine may have direct effects at the vasopressin receptor (Berrettini *et al.* 1981). It is also possible that some of the positive effects of carbamazepine on mood and cognition could be related to its vasopressin agonist-like effects.

Carbamazepine also has interesting effects on noradrenergic mechanisms both blocking re-uptake and inhibiting stimulated-induced release (Purdy *et al.* 1977). Recent studies suggest that it may decrease GABA turnover (Bernasconi & Martin, 1979), although CSF GABA levels in affectively ill patients are unaffected (Post *et al.* 1980). While it is highly effective in the treatment of a variety of pain syndromes, carbamazepine does not significantly affect CSF opiate binding activity (Post *et al.* 1981*a*). Rubinow and associates (1982) have reported that carbamazepine significantly decreases CSF somatostatin. Further laboratory and clinical investigations are needed to delineate the major mechanisms of action of carbamazepine in relation to its psychotropic, anticonvulsive, and antinociceptive effects.

Recently, Emrich and associates (1980) reported that another anticonvulsant, valproic acid, was useful in the treatment of a small number of patients with treatment-resistant affective illness. These findings, taken in conjunction with observations of carbamazepine's efficacy, raise the question of whether a series of anticonvulsant compounds may not have positive psychotropic effects in some patients with affective illness. We are currently studying whether patients who respond to carbamazepine will also respond to other anticonvulsants. In our first patient, who was an unequivocal carbamazepine responder on two occasions, no antimanic response was in evidence when she was crossed over on a double-blind basis to either phenytoin or valproic acid (Post *et al.* 1982*a*; unpublished data with W. Berrettini). The selectivity of response to anticonvulsant agents may yield further clues regarding their relative regional and biochemical mechanisms of action. In the light of the emerging evidence of positive responses to carbamazepine in primary and secondary affective syndromes and also perhaps to valproic acid in some individuals (Emrich *et al.* 1980), one might ask why seizures induced by electroconvulsive therapy are also efficacious in the treatment of manic and depresssive illness. A recent study in our laboratory, in collaboration with F. Putnam and N. Contel, suggests a possible explanation of the paradox that both seizures and anticonvulsant agents might be useful in the treatment of affective illness. We have observed that electroconvulsive seizures (ECS) markedly inhibited the development and maintenance of amygdala kindled seizures (Post *et al.* 1981*b*). ECS six hours prior to amygdala kindling inhibited the development of seizures when compared with sham ECS animals. In a further study, seven daily ECS compared with sham treatment suppressed amygdala kindled seizures for up to five days following the resumption of kindling. These data raise the possibility that the limbic anticonvulsant effects of electroconvulsive seizures could be, in part, related to their usefulness in the treatment of affectively ill patients.

We would encourage cautious clinical investigative work to delineate further clinical and biological markers of carabamazepine response, as well as approaches to underlying biochemical and physiological mechanisms of action. Although the drug in the United States is not approved by the Food and Drug Administration for use in patients with affective illness, it is available on the basis of a physician's discretion. Considerable experience has been gleaned in the long-term use of carbamazepine in patients with epilepsy (Penry & Daly, 1975). In this area, although there are rare reports of the development aplastic anaemia (Piscotta, 1975), recent experience has documented the safety of the drug and its record of good patient acceptance compared with other anticonvulsant agents. Ongoing studies of carbamazepine suggest the possibility that not only will it prove to be a new and clinically important form of treatment, particularly for patients not responsive or unable

to tolerate lithium carbonate, but also the drug might provide additional information for the understanding of the mechanisms underlying the major affective disorder (Post *et al.* 1982*b*).

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