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Carbamazepine and its 10,11-epoxide metabolite in acute mania: clinical and pharmacokinetic correlates

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Summary. The study was designed to investigate the antimanic profile of carbamazepine as a first-line drug in affective or schizoaffective disorders, to correlate the clinical efficacy with the plasma level of carbamazepine and its 10,11-epoxide metabolite, and to test the potential value of monitoring the salivary level. It was administered alone for 3 weeks to 21 acute manic inpatients. During the first week, the dosage was rapidly increased to 800 mg/day in order to produce steady-state plasma levels of carbamazepine on Day 7. The individual dose was then adjusted to maintain the therapeutic range of 8–12 mg/l. Plasma and saliva levels of the drug and its metabolite, as well as clinical status were assessed weekly.

Overall, there was 62% globally improved patients and 77% in affective disorders. The improvement of manic symptoms was significantly lower in schizoaffective than in affective disorders, whereas the dropout rate and the need for antipsychotic medication was higher in the former group.

The antimanic response was significantly correlated with the plasma levels both of carbamazepine and its epoxide metabolite, with a time-lag consistent with a delayed drug effect.

Drug and metabolite concentrations in saliva were close to their plasma free fraction and were strongly correlated with their plasma levels, suggesting the potential value of salivary drug monitoring.

Key words: Carbamazepine, Saliva, Mania; Carbamazepine epoxide, drug concentration, Concentration-response relationship, therapeutic monitoring

Carbamazepine is an anticonvulsant drug, chemically related to the tricyclic antidepressants. Since the clinical investigations by Okuma et al. (1973, 1979) and by Ballenger and Post (1978, 1980), carbamazepine has gained widespread use in psychiatry, particularly as an alternative to lithium salts in the pharmacotherapy of affective disorders [Ballenger, 1988]. Its mechanism of action is not clearly understood and both biological and neurophysiological hypotheses have been discussed [Post et al., 1984a].

The present investigation was performed: to evaluate the therapeutic profile of carbamazepine as a first-line drug in the management of acute manic episodes in affective as well as schizoaffective patients; to correlate clinical efficacy with the plasma levels of carbamazepine and its 10,11-epoxide metabolite, and to explore the potential value of saliva level monitoring.

Subjects and methods

Subjects

The subjects were newly admitted inpatients, aged 18–65 y, who were in hospital throughout the study. Patients met the DSM-III criteria for a manic episode and were diagnosed as having an affective or schizoaffective disorder. They gave informed consent to participation in the study. Patients with an organic brain syndrome, epilepsy, cardiovascular disease or haematological disorders, as well as pregnant women, were excluded.

Drug administration

Carbamazepine (Tegretol 200 mg tablets, Ciba-Geigy) was administered orally three times daily for 3 weeks, according to an open trial design. During the first week, starting with a daily dose of 400 mg/24 h on Day 1, all patients received the same increasing dosage up to 800 mg/24 h on Day 3, so as to obtain a steady-state plasma level of carbamazepine on Day 7. Then, the dosage was individually adjusted to maintain the therapeutic plasma level of carbamazepine 8–12 mg/l. Monotherapy was recommended. If necessary, droperidol (25–100 mg/24 h) could be prescribed (there is no evidence from the literature that droperidol affects carbamazepine pharmacokinetics). The need to prescribe droperidol and its dose and the duration of treatment were considered as indirect indications of the inefficacy of carbamazepine. No medication other than carbamazepine and droperidol was given to any patient.

Clinical evaluations

The patients were rated by the same physician before treatment, on Days 4 and 7, and then at weekly intervals, using the Bech-Rafaelsen Mania Scale [BRMS, Bech et al., 1979], and the Brief Psychiatric Rating Scale [BPRS, Pichot et al., 1967]. In addition, a global evalu-

Table 1. Plasma (P) and saliva (S) levels of carbamazepine (CBZ) and carbamazepine epoxide (CBZ-E)

Day	Dosage mg/kg per day	Medium	CBZ $mg \cdot l^{-1}$	CBZ-E $mg \cdot l^{-1}$	CBZ-E/CBZ ratio
4	11.3 (1.9)	Plasma (20)	9.0 (2.2)	1.8 (0.4)	0.21 (0.04)
7	11.2 (2.1)	Plasma (20)	8.6 (1.3)	1.9 (0.4)	0.22 (0.04)
		Saliva (14)	2.5 (0.7)	0.9 (0.4)	0.33 (0.19)
		S/P ratio (14)	0.30 (0.07)	0.44 (0.19)	
14	12.1 (3.7)	Plasma (17)	8.6 (2.1)	1.9 (0.8)	0.22 (0.04)
21	12.0 (2.7)	Plasma (16)	7.4 (1.6)	1.5 (0.8)	0.21 (0.08)
		Saliva (9)	2.4 (0.9)	0.7 (0.3)	0.34 (0.21)
		S/P ratio (9)	0.33 (0.06)	0.46 (0.18)	

Mean with (SD), n in parentheses.

Table 2. Clinical global improvement and dropouts in 21 patients with affective or schizoaffective disorders

Global improvement (Day 21)	Number of patients		
	Total 21	Affective disorders 13	Schizoaffective disorders 8
Absent	2	0	2
Poor	2	2	0
Marked	6	3	3
Complete	7	7	0
DROPOUTS	4	1	3

ation, taking into account the opinion of the attending nurse, was performed at each examination. That evaluation classified clinical improvement as 'complete, marked, poor or absent'.

Adverse effects were evaluated using a check-list of physical symptoms [Guelfi et al., 1983]. Laboratory tests of liver function, complete blood count and differential leukocyte count and blood ion concentrations in each patient were performed before treatment and weekly thereafter.

Determination of plasma and saliva concentrations

Plasma and saliva samples were obtained in the morning, just before the first dose of the day was taken, i.e. 12 h after the last dose. Blood 10 ml was collected in preheparinized vacuum tubes. Plasma was separated after centrifugation and a fraction was stored at −20 °C until analysed. Saliva was collected directly, without previous stimulation, and was stored in the same way.

Plasma and saliva levels of carbamazepine and its 10,11-epoxide metabolite were measured by reversed-phase HPLC after solvent demixing extraction, according to a previously described technique [Alric et al., 1984]. The detection limits, defined as a signal/noise ratio greater than 3, were 0.6 $mg \cdot l^{-1}$ and 0.4 $mg \cdot l^{-1}$ for carbamazepine and carbamazepine epoxide, respectively. Between-run reproducibility and within-run precision, both determined as coefficients of variation, were 4.4 % and 3.1 % respectively.

Data analysis

Frequencies of therapeutic responses and adverse reactions are expressed as the percentages of the number of patients included. Other results are expressed as mean with (SD). Data were submitted either to Student's t test or to analysis of variance and the Newman-Keuls multiple comparison test. Linear regression analysis was performed to correlate saliva and plasma drug levels, and the Spearman rank correlation (r_s) was used to study concentration-effect relationships.

Results

Twenty-one manic patients were included, 13 men (mean (SD) age 38 (18) y, range 18–65 y) and 8 women, (44 (17) y, range 20–60 y). According to DSM-III diagnostic criteria, 13 patients suffered from affective disorders (7 manic bipolar disorders, 2 cyclothymic disorders and 4 atypical bipolar disorders) and 8 patients from schizoaffective disorders. Four patients (1 manic bipolar and 3 schizoaffective disorders) did not complete the clinical trial, due to the need for antipsychotic medication.

Dose and plasma and saliva levels of carbamazepine and carbamazepine epoxide

Mean dose and drug levels are shown in Table 1. The daily dose of carbamazepine overall ranged between 0.3–1.2 $g \cdot 24\ h^{-1}$ (mean 800 $mg \cdot 24\ h^{-1}$). Carbamazepine was used without droperidol except in 2 bipolar affective patients and 5 schizoaffective patients (3 of the latter dropped out). The mean daily dose of droperidol was 35 mg (range 5–90 mg) and the mean duration of its prescription was 11 days (range 1–21 d).

Carbamazepine and carbamazepine epoxide levels in plasma ranged between 4.5–14.1 $mg \cdot l^{-1}$ and 0.5–3.1 $mg \cdot l^{-1}$, respectively. Only one patient had a carbamazepine level below 8 $mg \cdot l^{-1}$ throughout the study, although some patients occasionally displayed carbamazepine levels lower than 8 $mg \cdot l^{-1}$. This was ascribable to poor clinical tolerance and the consequent need to reduce the dose. The plasma metabolite/parent drug ratio was remarkably stable (21–22 %) during the treatment, and there was no significant difference according to age and sex (not shown).

Carbamazepine and its epoxide in saliva on Days 7 and 21 were within the range of 0.7–4.2 and 0.2–1.8 $mg \cdot l^{-1}$ re-

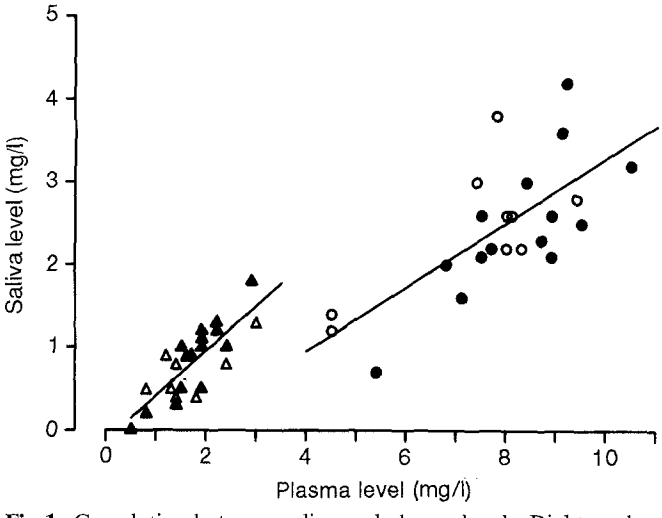

Fig. 1. Correlation between saliva and plasma levels. Right: carbamazepine (• Day 7, ○ Day 21), $n = 23$, $r = 0.71$, $P < 0.001$. Left: carbamazepine epoxide (▲ Day 7, △ Day 21), $n = 23$, $r = 0.79$, $P < 0.001$

Table 3. Time course of improvement score in carbamazepine-treated patients

	Baseline score		Percent improvement score							
	Day 0		Day 4		Day 7		Day 14		Day 21	
	BRMS	BPRS	BRMS	BPRS	BRMS	BPRS	BRMS	BPRS	BRMS	BPRS
Affective disorders	18.4 (13) (3.6)	28.9 (5.8)	23.6 (13) (17.3)	37.2 (19.8)	44.4 (12) (26.7)	53.2 (21.8)	59.3 (12) (27.0)	66.3 (21.8)	81.1** (12) (14.9)	69.4 (40.9)
Schizoaffective disorders	19.0 (8) (3.4)	32.6 (8.2)	25.3 (8) (13.3)	19.1 (34.5)	42.6 (8) (30.8)	44.4 (35.6)	68.7 (7) (13.0)	36.0 (47.6)	61.8 (5) (20.6)	40.4 (42.3)
Total	18.6 (21) (3.7)	30.3 (6.9)	24.2 (21) (15.6)	30.3 (27.0)	43.7 (20) (27.7)	49.7 (27.7)	62.7* (19) (22.7)	55.1 (35.7)	75.4*** (17) (18.6)	60.9 (42.1)

Mean with (SD), n in parentheses.
BRMS = Beach-Rafaelsen Mania Scale. BPRS = Brief Psychiatric Rating Scale.
* $P < 0.01$, significantly different from BRMS improvement score on Day 7.
** $P < 0.02$, significantly different from BRMS improvement score in schizoaffective patients.
*** $P < 0.001$, significantly different from BRMS improvement score on Day 7.

spectively. In both cases, the salivary level was significantly correlated with the plasma level ($r = 0.71$ and $r = 0.79$, respectively; $P < 0.001$; Fig. 1).

Efficacy

Global improvement rates at the conclusion of carbamazepine treatment are shown in Table 2. As dropouts were ascribed to a lack of therapeutic effect, they are included in the analysis of efficacy. The number of markedly or completely improved cases was 13/21 (62%), comprising 10/13 (77%) and 3/8 (38%) in patients with affective or schizoaffective disorders. With regard to the time course of the weekly global improvement rating, the percentage of markedly or completely improved cases increased between Days 7 (24%) and 14 (62%), suggesting that the onset of the therapeutic effect occurred during the second week of treatment in most of the patients.

The mean (SD) baseline score of all 21 patients on the Bech-Rafaelsen Mania Scale was 18.6 (3.7). Carbamazepine led to a marked decrease in manic symptoms. The improvement score on the BRMS, defined as change in score as a percentage of baseline score, significantly increased with time, reaching 75.4 (18.6)% ($n = 17$) on Day 21 (Table 3), and second, it differed significantly ($P < 0.02$) between affective and schizoaffective disorders, 81.1 (14.9)% ($n = 12$) and 61.8 (20.6)% ($n = 5$), respectively.

No correlation was found between the clinical status and the plasma drug concentration at the same time. However, clinical improvement in manic symptoms on Day 21 was significantly correlated with plasma levels of carbamazepine ($r_s = 0.67$, $P < 0.02$) and carbamazepine epoxide ($r_s = 0.63$, $P < 0.02$) on Day 7 (Fig. 2). There was also a significant correlation ($r_s = 0.49$, $P < 0.05$) between efficacy on Day 14 and plasma drug level on Day 7 (not shown). Combining carbamazepine and carbamazepine epoxide levels did not affect these concentration-effect relationships, but it did enhance the correlations. On the other hand, the clinical effect was not significantly correlated with the salivary drug concentration.

Adverse reactions

The adverse effects encountered were those generally expected with carbamazepine. Their frequency was fairly high (a total of 54 somatic complaints were recorded), particularly in the initial phase of the treatment: 38 (70.4%) during the first week versus 16 (29.6%) during the last 2 weeks. Adverse effects were reported by 76% of

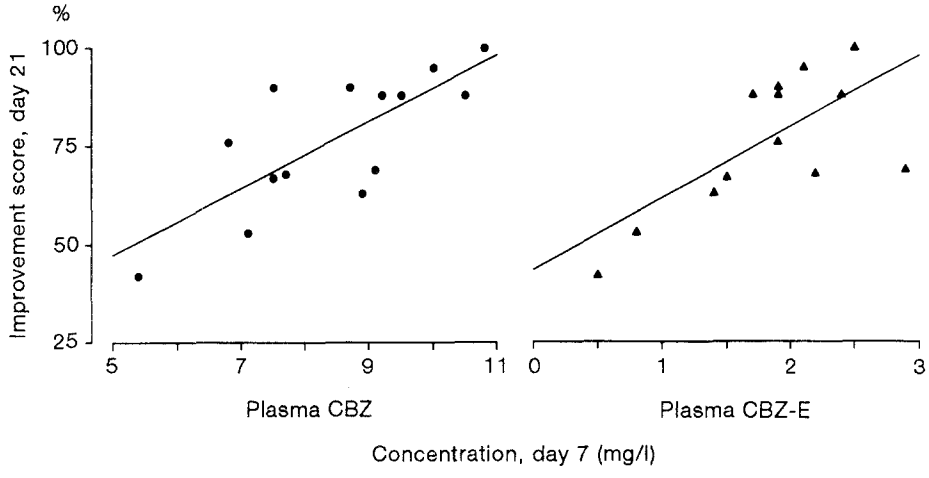

Fig. 2. Concentration-response relationships. The improvement score is expressed as the change in score as a percentage of the baseline score on the Bech-Rafaelsen Mania Scale. Left panel: correlation with plasma carbamazepine (CBZ), $n = 14$, $r_s = 0.67$, $P < 0.02$. Right panel: correlation with plasma carbamazepine-epoxide (CBZ-E), $n = 14$ $r_s = 0.63$, $P < 0.02$. n represents the number of patients who completed the 21-day treatment, excluding 3 transiently non-compliant patients. The regression lines were drawn according to the results of linear regression analysis, which also yielded significant correlations

Table 4. Most common side effects of carbamazepine treatment

	Percentage of the 21 patients
Symptoms	
Dizziness	42.9
Asthenia	23.8
Nausea	23.8
Blurred vision	19
Pruritus	19
Drowsiness	14.3
Headache	14.3
Vomiting	14.3
Abnormal laboratory findings	
Gamma GTP	19
Plasma sodium	9.5
GPT	4.8
Leukocyte count	4.8

the patients. Only 3 patients who completed the trial did not relate any side effect. Nevertheless, none of the dropouts was due to an adverse reaction. Abnormal laboratory findings, which were judged as possibly related to carbamazepine, were observed in 6 cases. The most common adverse-effects are reported in Table 4. There was no clear relationship between the side effects and the plasma level of carbamazepine or its epoxide.

Discussion

Clinical data

In the present study, the percentage of completely or markedly improved manic patients was 62% overall, and 77% in patients with affective disorders. In controlled studies against chlorpromazine, Okuma et al. (1979) found that carbamazepine improved symptoms in 70% of the patients; Grossi et al. (1984) reported an improvement rate of 67%. In a control study against placebo, 78% of the patients had a positive antimanic response to carbamazepine [Ballenger and Post, 1980], and 75% were improved in a comparative study with haloperidol [Brown et al., 1989]. Thus the findings concerning antimanic efficacy are very close to those previously reported in double blind studies [Cookson, 1988; Ballenger, 1988].

In the present study of carbamazepine monotherapy, the global improvement rate for schizoaffective disorders was lower than that for affective disorders, only 38% of the schizoaffective patients being markedly improved; furthermore, both the dropout rate and the need for antipsychotic medication were higher in this group. On the other hand, the improvement score in manic symptoms was significantly lower in schizoaffective than in affective disorders. These results differ from some clinical reports suggesting that carbamazepine may be more effective in the treatment of mood disorders with schizoaffective features [Azorin et al., 1986; Placidi et al., 1986], psychotic or schizoaffective features being proposed as predictive factors of the efficacy of carbamazepine in manic states [Ballenger, 1988]. However, carbamazepine has not always been used in monotherapy. The present results are in accordance with a previous controlled study by Stoll et al. (1985), in which 75% of manic patients versus 54% of schizoaffective patients were improved after carbamazepine treatment. In a more recent open trial, the efficacy in these two diagnostic groups was 73% and 62%, respectively [Okuma et al., 1989]. The therapeutic effect of carbamazepine on schizoaffective disorders could be attained through the control of affective excitement. Therefore, it might be suggested that combination of carbamazepine with an antipsychotic drug might be a valuable treatment for schizoaffective disorders, as indicated by the work of Klein et al. (1984).

The clinical or biological adverse reactions encountered here were similar to those previously reported [Ballenger and Post, 1980; Sillanpää, 1981; Okuma et al., 1989]. However, although easily manageable, and in no case the reason for stopping the drug, their incidence was fairly high, particularly dizziness and nausea. This result can probably be ascribed to the rapid increase in dose, and so it could limit clinical interest in carbamazepine alone in the treatment of acute manic episodes. On the other hand, the percentage of drowsiness was very close to previously reported data [Ballenger and Post, 1980; Okuma et al., 1989] and the effectiveness of the drug appeared to be independent of marked sedation.

Analytical data and the plasma drug concentration-response relationships

Plasma levels of carbamazepine were within the accepted therapeutic range for affective disorders [Ballenger, 1988; Cookson, 1988], which is also the range for the treatment of epilepsy [Choonara and Rane, 1990]. The changes in mean daily dose and in plasma concentrations throughout the protocol is in accordance with the enzyme inducing properties of carbamazepine. The carbamazepine-epoxide/carbamazepine ratio was quite close to values reported when carbamazepine was used alone [Ramsay et al., 1990].

With regard to the concentration-response relationship, no correlation has previously been found between clinical efficacy and the plasma levels of either carbamazepine or carbamazepine epoxide [Azorin et al., 1988]. Post et al. (1983) found that carbamazepine levels in plasma or in CSF were not related to the degree of antidepressant or antimanic response. In contrast, CSF concentrations of carbamazepine epoxide were correlated with the degree of antidepressant response, and there was a similar trend for degree of improvement to be correlated with the plasma 10,11-epoxide concentration [Post et al., 1983; 1984b]. In the present study, the antimanic response was correlated with the pre-monitoring steady-state plasma carbamazepine level on Day 7 only after two or three weeks of treatment. This time-lag is consistent with delayed drug effectiveness. Indeed, for most of the patients, significant improvement occurred during the second week of treatment, which is in accordance with the previously reported onset of therapeutic activity [Okuma et al., 1979]. Furthermore, the therapeutic effect became significantly strengthened throughout the 3-week treatment period. On the other hand, the lack of a concentration-re-

sponse correlation on Days 14 and 21 could be ascribed to the trial design itself, which, after the first week, permitted drug monitoring and dosage adjustment so as to maintain the desired therapeutic range. The improvement score was also correlated with the plasma level of carbamazepine-10,11-epoxide, which would be expected since the metabolite level was directly related to the carbamazepine level. However, this result, together with the stronger concentration-effect correlation found when combining carbamazepine and its metabolite levels, could be consistent with potential antimanic activity of the metabolite, in addition to its previously reported anticonvulsant effect in animals [Frigerio and Morselli, 1975; Albright and Bruni, 1984], as well as its antineuralgic effect in man [Tomson and Bertilsson, 1984].

In the present study, as indicated by the saliva/plasma ratio, salivary levels of carbamazepine and its epoxide metabolite were in accordance with the known plasma free fraction. Saliva is a low protein fluid, and drug concentrations in it may reflect the level of unbound drug, as already documented [McAuliffe et al., 1977; McKichan et al., 1981]. Clinical improvement was not correlated with the salivary level of carbamazepine, which might have been due to the inadequate number of patients represented, due to the technical difficulties in sampling saliva without stimulation. However, when considering a moderately bound drug such as carbamazepine, the free fraction may not give a better lead to drug effect than the total plasma concentration. Finally, salivary concentrations were strongly correlated with plasma levels, and the range of concentrations of carbamazepine in saliva here was close to the therapeutic range suggested by previous studies [McKichan et al. 1981; Rylance and Moreland, 1981]. As the collection of saliva does not involve venepuncture, monitoring drug concentrations in it could be of value for some patients, especially as carbamazepine treatment is often prolonged and requires therapeutic monitoring.

In conclusion, the results showed that carbamazepine alone could be used as a first-line drug in acute manic episodes, provided that the rapid increase in dose required by the emergency was well tolerated. This monotherapy schedule appeared to be of limited value in schizoaffective patients. Clinical improvement in manic symptoms was significantly correlated with plasma levels both of carbamazepine and its epoxide metabolite, with a time-lag consistent with a delayed drug effect. The results suggest the potential value of monitoring the drug level in saliva.

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