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# Inhibition by erythromycin of the conversion of carbamazepine to its active 10,11-epoxide metabolite

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The serum levels of carbamazepine (CBZ) and its 10,11-epoxide metabolite (CBZ-E) were determined in seven subjects after a single dose of CBZ (400 mg) in the control state and during co-administration of erythromycin (500 mg three times daily for 10 days). Erythromycin treatment was associated with a decrease in CBZ clearance and a prolongation of CBZ half-life, while CBZ-E levels were markedly reduced. These data provide evidence that erythromycin inhibits the conversion of CBZ to its epoxide metabolite.

**Keywords** carbamazepine carbamazepine-10,11-epoxide erythromycin drug interaction

## Introduction

Administration of erythromycin to carbamazepine (CBZ)-treated patients can increase serum CBZ levels and precipitate clinical signs of CBZ intoxication (Berrettini, 1986; Carranco *et al.*, 1985; Goulden *et al.*, 1985; Hedrick *et al.*, 1983; Jaster & Abbas, 1986; Mesdjian *et al.*, 1980; Vaida & Bladin, 1984; Wroblewski *et al.*, 1986). Although this interaction is generally considered to be due to inhibition of CBZ metabolism (Wong *et al.*, 1983), no metabolite measurements have been made to support such an hypothesis. Knowledge of the effect of erythromycin on CBZ biotransformation is also important because CBZ is largely converted to the pharmacologically active 10,11-epoxide metabolite (CBZ-E) (Bertilsson & Tomson, 1986) and some drugs which precipitate clinical signs of CBZ intoxication may do so in full (Pisani *et al.*, 1986a) or in part (Pisani *et al.*, 1986b) by increasing CBZ-E levels.

In the present study we have evaluated serum CBZ and CBZ-E levels after a single dose of CBZ given in the presence and in the absence of erythromycin therapy.

## Methods

Seven normal male subjects aged 21–27 years (weight 70–90 kg) received a single oral dose of CBZ (400 mg) 1 h after a light breakfast on two randomized occasions separated by a 3-week interval: a) in the absence of associated drugs and b) on the seventh day of treatment with erythromycin stearate, 500 mg (as base) three times daily orally for 10 days. The study was approved by a local Ethics Committee.

The concentration of CBZ and CBZ-E in serum samples collected after CBZ dosing was determined by an h.p.l.c. method modified from Sawchuk & Cartier (1982). Kinetic analysis was performed by standard methods (Perucca *et al.*, 1978); estimates of clearance and volume of distribution assume complete bioavailability (Wong *et al.*, 1983).

Statistical comparisons were made by using the Student's *t*-test for paired data.

## Results

Serum level profiles of CBZ and CBZ-E in the presence and in the absence of erythromycin treatment are illustrated in Figure 1, while calculated kinetic parameters are summarized in Table 1. Carbamazepine absorption was not apparently affected by erythromycin, peak serum

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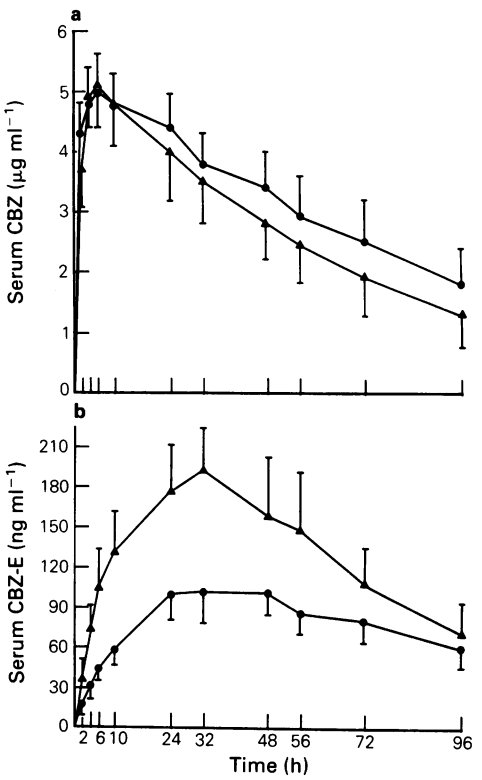


**Figure 1** a) Carbamazepine (CBZ) and b) carbamazepine-10,11-epoxide (CBZ-E) serum concentration curves (means ± s.d.) in the absence (▲) and in the presence (●) of erythromycin co-administration. Differences between study occasions were statistically significant ($P < 0.01$) at all times between 24 and 96 h for CBZ and between 2 and 48 h for CBZ-E.

CBZ levels and times to peak being identical in the two occasions. By contrast, erythromycin treatment was associated in all subjects with a moderate prolongation of the CBZ elimination half-life ($P < 0.01$) and a reduction of CBZ clearance ($P < 0.01$).

Serum CBZ-E levels were markedly reduced by co-administration of erythromycin (Figure 1), with a highly significant decrease in AUC values for the metabolite.

## Discussion

The present study confirms previous observations that erythromycin elevates serum CBZ levels: although the magnitude of the increase was relatively small, the effect was consistent in all subjects investigated. Since CBZ is eliminated virtually entirely by hepatic metabolism (Bertilsson & Tomson, 1986), the clearance changes after erythromycin can reasonably be explained only in terms of inhibition of metabolism. Alternative mechanisms such as increased absorption or increased protein binding may also induce a similar change in apparent 'oral' clearance, but would not explain the prolongation of CBZ half-life in the presence of an unchanged volume of distribution. The observation that serum metabolite levels were markedly depressed during erythromycin administration strongly suggests that the impairment of CBZ metabolism is accounted for at least in part by inhibition of the pathway leading to formation of the epoxide.

As shown in Figure 1, there is a clear discrepancy between the erythromycin-induced changes in CBZ kinetics, which were relatively small,

**Table 1** Kinetic parameters (mean ± s.d., $n = 7$) of carbamazepine and carbamazepine-10, 11-epoxide in the absence (control session) and in the presence of erythromycin co-administration

| | *Control session* | *During erythromycin* | P *value* |
|---|---|---|---|
| *Carbamazepine* | | | |
| $C_{max}$ (μg ml$^{-1}$) | 5.2 ± 0.5 | 5.0 ± 0.6 | NS |
| $t_{max}$ (h) | 5.4 ± 0.6 | 5.7 ± 2.4 | NS |
| $t_{1/2}$ (h) | 42.4 ± 10.2 | 56.2 ± 17.4 | < 0.01 |
| AUC(0–∞) (μg ml$^{-1}$ h) | 362.9 ± 101.3 | 478.9 ± 151.4 | < 0.01 |
| $V$ (1 kg$^{-1}$) | 0.84 ± 0.09 | 0.87 ± 0.06 | NS |
| CL (ml kg$^{-1}$ h$^{-1}$) | 14.9 ± 3.8 | 11.3 ± 2.7 | < 0.01 |
| *Carbamazepine-10, 11-epoxide* | | | |
| $C_{max}$ (ng ml$^{-1}$) | 183.9 ± 41.1 | 107.4 ± 19.1 | < 0.01 |
| $t_{max}$ (h) | 26.3 ± 3.9 | 30.9 ± 8.6 | NS |
| AUC(0–96) (μg ml$^{-1}$ h) | 12.5 ± 2.7 | 7.8 ± 1.1 | < 0.001 |

$C_{max}$ = peak concentration; $t_{max}$ = time to peak concentration; $t_{1/2}$ = half-life; AUC = area under the serum concentration; CL and $V$ = apparent clearance and volume of distribution respectively.

and the marked depression in the levels of the active epoxide metabolite. This finding suggests that the alternative routes of CBZ metabolism not involving the epoxide-diol pathway (Bertilsson & Tomson, 1986) are not importantly hindered by erythromycin. If this interpretation is correct, the changes in CBZ kinetics after erythromycin would be expected to be more marked in patients stabilized on chronic CBZ therapy, in whom induction of the epoxide pathway leads to a much greater proportion of the dose being converted to CBZ-E (Bertilsson & Tomson, 1986), than in subjects given a single dose of CBZ for the first time. Indeed, available evidence does support this suggestion. While the only other study examining the effect of erythromycin on the single dose kinetics of CBZ (Wong *et al.*, 1983) produced results very similar to ours, i.e. only a moderate decrease in CBZ clearance, several reports indicate that in chronically CBZ-treated patients erythromycin can cause an up to 100–200% increase in plasma CBZ levels (Berrettini, 1986; Carranco *et al.*, 1985; Hedrick *et al.*, 1983; Jaster & Abbas, 1986; Vaida *et al.*, 1984; Wroblewski *et al.*, 1986).

From the clinical point of view, our data suggest that the manifestations of toxicity observed when the two drugs are combined can be ascribed virtually entirely to unchanged CBZ. In this respect, the interaction caused by erythromycin partly resembles that seen with propoxyphene (Dam *et al.*, 1977), verapamil (Macphee *et al.*, 1986) and danazol (Kramer *et al.*, 1986), which also raise the CBZ/CBZ-E ratio in serum, but differs from that caused by viloxazine, which increases the serum concentration of both CBZ and CBZ-E (Pisani *et al.*, 1986b) or from that caused by valproic acid and valpromide, which precipitate intoxication by selectively increasing CBZ-E levels (Pisani *et al.*, 1986a).

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