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The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites

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Steady state metabolite/parent drug plasma ratios were measured in 15 epileptic patients on carbamazepine (CBZ) monotherapy and in seven patients treated with CBZ and clobazam (CLB). CBZ plasma concentrations did not differ between the two groups but patients also treated with CLB exhibited higher concentrations of CBZ-10,11-epoxide (CBZ-E) and trans-10,11-dihydro-10,11-dihydroxy-CBZ (CBZ-T). Ratios between all of the metabolites of CBZ and the parent compound were higher in patients on polytherapy but the ratio between metabolites was not different. CLB comedication causes a moderate increase (about 1.5-fold) in CBZ metabolism, probably by inducing its epoxidation.

Keywords clobazam carbamazepine carbamazepine-epoxide carbamazepine-diol drug interactions

Introduction

Clobazam (CLB) is a 1,5-benzodiazepine commonly used as adjunct therapy in the treatment of resistant epilepsy (Callaghan & Goggin, 1988; Robertson, 1986). It is metabolized to *N*-desmethylclobazam, which has also been successfully used in the treatment of refractory epilepsy (Haigh *et al.*, 1987). CLB is often used in conjunction with carbamazepine (CBZ), a first line anticonvulsant which has hetero- and auto-inducing properties (Bertilsson & Tomson, 1986).

CBZ is metabolized mainly to carbamazepine-10,11-epoxide (CBZ-E) which, in turn, is converted to trans-10,11-dihydro-10,11-dihydroxy-carbamazepine (CBZ-T) by epoxide hydrolase (Tomson *et al.*, 1983). Whereas CBZ-T has no pharmacological properties, CBZ-E adds to the therapeutic effect of the parent drug (Bourgeois & Wad, 1984*a*; Tomson & Bertilsson, 1984).

It has been shown that CBZ coadministration increases the metabolism of CLB (Levy *et al.*, 1983), but the effect of CLB on CBZ metabolism has not been investigated.

The present study was undertaken to assess the effect of CLB on CBZ metabolism from measurements of metabolite/CBZ ratios.

Methods

Twenty-two epileptic patients treated with CBZ either as monotherapy ($n = 15$) or in combination with CLB (30 mg/daily) ($n = 7$) were studied. Each patient had been taking CBZ according to the same schedule for more than 3 weeks.

Concentrations of CBZ and its metabolites were measured by h.p.l.c. as described previously (Macphee *et al.*, 1984) with minor modifications. Thus, samples were reconstituted in 100 μl mobile phase (water/methanol/acetonitrile: 58/22/20 v/v/v) injected onto a Brownlee Labs. 5 μm RP-18 column, and detection was at 215 nm.

Differences between groups were analyzed by the Mann-Whitney U test and the null hypothesis was rejected when $P < 0.05$.

Results

The dosage of CBZ and plasma concentrations of the parent drug and its metabolites with and without concurrent administration of CLB are shown in Table 1, expressed as quartiles. Although patients on monotherapy received a significantly lower dose of CBZ, the plasma

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Table 1 Quartiles (Q_1, median, Q_3) of doses and plasma concentrations of carbamazepine (CBZ), carbamazepine-10,11-epoxide (CBZ-E) and trans-10,11-dihydro-10,11-dihydroxy-carbamazepine (CBZ-T) in patients on CBZ monotherapy or also treated with clobazam (CLB).

		Dose ($g\,day^{-1}$)	*CBZ* ($\mu g\,ml^{-1}$)	*CBZ-E* ($\mu g\,ml^{-1}$)	*CBZ-T* ($\mu g\,ml^{-1}$)
CBZ	Median	0.8	6.1	0.7	1.6
	Q_1–Q_3	0.6–1.2	4.7–8.0	0.5–1.2	1.7–2.9
CBZ + CLB	Median	1.2**	7.4	1.3*	4.2**
	Q_1–Q_3	1.2–1.6	6.7–7.4	1.1–2.5	3.2–4.3

Differences *vs* patients on monotherapy (Mann-Whitney U test): * $P < 0.05$; ** $P < 0.01$

Table 2 Quartiles (Q_1, median, Q_3) of metabolite/parent compound ratios for the steady-state plasma concentrations of carbamazepine (CBZ), carbamazepine-10,11-epoxide (CBZ-E) and trans-10,11-dihydro-10,11-dihydroxy-carbamazepine (CBZ-T) in patients treated with CBZ alone or coadministered with clobazam (CLB)

		CBZ-E/CBZ (%)	*CBZ-T/CBZ* (%)	*CBZ-T/CBZ-E* (%)
CBZ	Median	12.7	27.5	216
	Q_1–Q_3	10.1–16.3	22.1–39.6	148–373
CBZ + CLB	Median	18.6**	51.1*	295
	Q_1–Q_3	17.0–20.4	37.4–59.6	172–321

Differences *vs* patients on monotherapy (Mann-Whitney U test): * $P < 0.05$; ** $P < 0.01$

concentrations of the drug were similar in both groups of patients. CBZ-E and CBZ-T concentrations were significantly higher in the group treated with CBZ and CLB.

Three different metabolite/parent drug ratios were calculated and the observed values are shown in Table 2 as quartiles. Whereas the ratio between each one of the metabolites of CBZ and the parent compound was significantly higher in the patients also treated with CLB, the ratio CBZ-T/CBZ-E was unaffected by comedication.

Discussion

Whilst 75% of our patients on monotherapy were receiving a dose of CBZ equal to or lower than 1200 mg 24 h^{-1}, only 25% of patients treated concomitantly with CLB were receiving this low a dose. This difference could be due either to a requirement for higher doses in patients with refractory epilepsy or to an inductive effect of CLB on CBZ. As plasma CBZ concentrations did not differ between the two groups of patients, the latter explanation seems the more likely.

When trying to evaluate the clearance of the parent drug by means of the ratio between steady-state plasma concentrations of a metabolite and the parent compound, the ratio between the fraction of the dose of parent drug metabolized to the metabolite under consideration and metabolite clearance is assumed to be a constant (van Belle & Friel, 1986). This is not the case for CBZ as the fraction of the dose metabolized through the epoxide–diol pathway ranges from 0.2 to 0.6 in patients (Bertilsson & Tomson, 1986). In spite of this, CBZ-E/CBZ (Brodie *et al.*, 1983; Macphee *et al.*, 1986; Patel *et al.*, 1981) and CBZ-T/CBZ ratios (Bourgeois & Wad, 1984b) are considered to be sensitive indicators of enzyme induction or inhibition.

It has been suggested that the steady-state serum CBZ-T/CBZ ratio is a more sensitive index of CBZ metabolism than CBZ-E/CBZ or CBZ-T/CBZ-E ratios (Bourgeois & Wad, 1984b). However, whenever epoxide hydrolase is not induced or, as occurs with phenobarbitone (Patel *et al.*, 1981), when induced, the rate of CBZ-E formation exceeds that of its elimination, CBZ-E/CBZ and CBZ-T/CBZ ratios should provide similar information. On the other hand, dissimilar results with these two ratios might be observed if epoxide hydrolase were inhibited, as occurs after the administration of valpromide (Pisani *et al.*, 1988).

The balance between CBZ-E formation and elimination can be assessed from the CBZ-T/CBZ-E ratio. This was not different in patients

taking CLB and those on monotherapy. Therefore, it was expected that both CBZ-E/CBZ and CBZ-T/CBZ ratios would be modified to the same extent, as was indeed observed.

The increases in CBZ-E/CBZ and CBZ-T/CBZ ratios (1.46 and 1.86 fold, respectively) suggest that CLB coadministration slightly increases the metabolism of CBZ, probably by induction of its epoxidation.

CBZ and CLB are both metabolized by oxidative pathways, which can be induced by the concomitant administration of other anticonvulsants (Brodie *et al.*, 1983; Jawad *et al.*, 1984) or inhibited by cimetidine (Macphee *et al.*, 1984; Pullar *et al.*, 1987). Within the superfamily of cytochrome P-450, overlapping substrate specificity is common. Therefore, while two substrates may not be metabolized predominantly by the same isoenzyme, they could still interfere with each other's metabolism.

The ratio *N*-desmethylclobazam/CLB has been used to study the inductive effect of CBZ on CLB metabolism. Thus, Levy *et al.* (1983) observed that CBZ comedication caused a 4-fold increase of this metabolite/parent drug ratio.

While self-induction of CLB metabolism seems unlikely (Greenblatt *et al.*, 1983), our results suggest that CLB has heteroinducing properties, as it significantly induces CBZ metabolism. Whether such an effect extends to CLB or to any of its metabolites, e.g. *N*-desmethylclobazam, should be investigated.

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