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CARBAMAZEPINE 10, 11 EPOXIDE CONCENTRATIONS IN EPILEPTICS ON CARBAMAZEPINE ALONE AND IN COMBINATION WITH OTHER ANTICONVULSANTS

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Steady state carbamazepine (CBZ) plasma concentrations were similar in 15 epileptics receiving monotherapy and in 24 patients taking CBZ in combination with one other anticonvulsant. The ratio of CBZ 10, 11-epoxide (CBZ-E) to the parent drug was significantly higher ($P < 0.01$) in those patients taking concomitant phenytoin ($n = 9$), phenobarbitone or primidone ($n = 9$), and valproic acid ($n = 6$) than in the patients receiving CBZ alone. In the monotherapy group, there was a significant correlation between CBZ-E/CBZ ratio and the concentration of the parent drug ($P < 0.05$). If CBZ-E has equipotent anticonvulsant properties to CBZ in man as is the case in animal models, routine CBZ-E concentrations may provide further refinement in the therapeutic drug monitoring of CBZ.

Keywords epilepsy carbamazepine carbamazepine 10, 11 epoxide

Introduction

Carbamazepine (CBZ) is a first line drug in the management of generalised tonic-clonic and partial epilepsy. It is metabolised to a number of more polar products largely by processes involving epoxidation and peroxidation (Eichelbaum & Bertilsson, 1975; Lertratanangkoon & Horning, 1982). Its major metabolite is CBZ 10, 11-epoxide (CBZ-E) (Pynnonen, 1979). Unlike many epoxides it is not rapidly decomposed and is present in identifiable amounts in the brain and CSF following chronic CBZ dosing (Johannssen *et al.*, 1976; Morselli *et al.*, 1977; Friis *et al.*, 1978). In various animal models CBZ-E has been shown to possess equipotent anticonvulsant properties to the parent drug (Frigerio & Morselli, 1975; Morselli *et al.*, 1975). It has been suggested that CBZ-E concentrations are higher in patients receiving combination anticonvulsant therapy than those on CBZ alone (Rane *et al.*, 1976; Pynnonen *et al.*, 1978; Westenberg *et al.*, 1978; McKauge *et al.*, 1982).

In this study we report steady state CBZ/CBZ-E ratios in 39 patients taking CBZ either alone or in combination with phenytoin (DPH), phenobarbitone (PB) or primidone (PRIM), and valproic acid (VPA).

Methods

Venous blood samples were obtained from 39 patients with epilepsy at a routine clinic visit. Each patient had been taking CBZ either alone or in combination with one other anticonvulsant in the same dose for more than 3 months. No patient was taking any other drug chronically. The blood was withdrawn into heparinised tubes, centrifuged immediately and stored at −20°C until analysis. CBZ and CBZ-E concentrations were obtained by a modification of the h.p.l.c. methodology outlined by Meijer (1981). Lower limit of detection for the CBZ-E assay was 0.2 ml l^{-1} which had a coefficient of variation of < 5%. This assay also provided clearly identifiable peaks for DPH, PB and PRIM. VPA concentrations were obtained by enzyme immunoassay (EMIT, SYVA).

Statistical analyses were performed using the Mann-Whitney U test (one-tailed) and correlations obtained by the Spearman ranking procedure.

Results

Mean CBZ dosages, CBZ and CBZ-E concentrations for each patient group are shown in Table 1. There were no significant differences in dosage or CBZ concentration between the monotherapy and any of the combination therapy groups. CBZ-E concentrations were higher in all the combined groups than in the patients taking CBZ alone. The difference was greater in those patients taking CBZ and VPA ($P <$

Table 1 Mean (± s.e. mean) and ranges of carbamazepine (CBZ) dosages and concentrations and carbamazepine 10-11-epoxide (CBZ-E) concentrations in patients taking CBZ alone or in combination with one other anticonvulsant

Drugs	n	*CBZ dosage (mg day^{-1})*	*CBZ concentration (mg l^{-1})*	*CBZ-E-concentration (mg l^{-1})*
CBZ alone	15	667 ± 78	6.76 ± 0.66	0.79 ± 0.12
Range		(300–1400)	(2.7–10.8)	(0.2–1.85)
CBZ + DPH	9	689 ± 90	6.3 ± 0.92	1.44 ± 0.27
Range		(300–1200)	(3.0–11.2)	(0.56–2.9)
CBZ + PB or PRIM	9	611 ± 81	6.73 ± 0.85	1.35 ± 0.27
Range		(300–1000)	(3.0–11.1)	(0.3–2.8)
CBZ + VPA	6	600 ± 73	7.3 ± 0.79	1.48 ± 0.26
Range		(400–800)	(5.0–10.3)	(0.75–2.6)

DPH = Phenytoin; PB = Phenobarbitone; PRIM = Primidone; VPA = Valproic acid

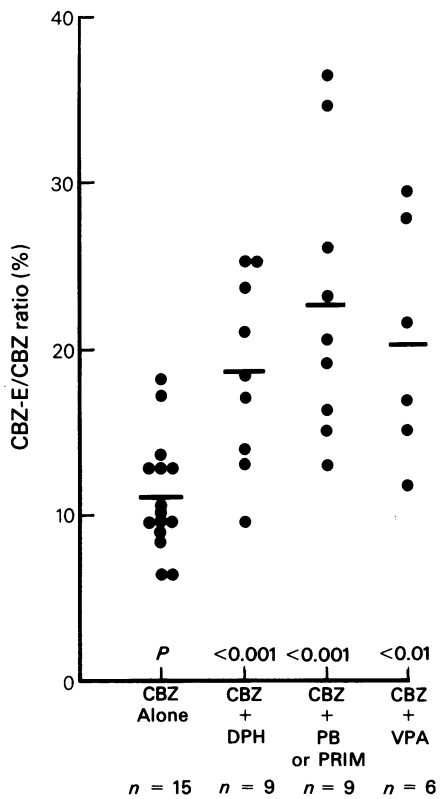

Figure 1 Ratio of carbamazepine 10-11-epoxide (CBZ-E) steady-state concentrations to that of carbamazepine (CBZ) in 15 patients taking CBZ alone, nine taking CBZ with phenytoin (DPH), nine with phenobarbitone (PB) or primidone (PRIM) and six with valproic acid (VPA). Statistics by Mann Whitney U test (one-tailed).

0.001) than those receiving concomitant DPH ($P < 0.05$) and PB or PRIM ($P < 0.025$).

CBZ-E/CBZ ratios for all four groups are shown in Figure 1 and were highly significantly elevated in all combination groups in comparison with the monotherapy patients. There was a significant correlation between CBZ concentration and CBZ-E/CBZ ratios in the monotherapy group ($r = 0.56$, $P < 0.05$) but such a correlation was not demonstrable in the 3 other groups when all data were combined. Concentrations of the other anticonvulsants ranged widely (DPH: 4.6–33.2 mg l^{-1}; PB: 4.6–38.7 mg l^{-1}; VPA: 21–94 mg l^{-1}) but there were no significant correlations between these values and the CBZ-E concentrations or CBZ-E/CBZ ratios.

Discussion

In previous studies in relatively small numbers of epileptics, CBZ–E/CBZ ratios have been shown to be higher when CBZ is taken concomitantly with DPH, PB or PRIM (Rane *et al.*, 1976; Pynnonen *et al.*, 1978; Westenberg *et al.*, 1978; McKauge *et al.*, 1981). We have confirmed these findings in patients taking no other medication chronically. The data from patients receiving PB and PRIM have been combined as PB is a major metabolite of PRIM. Current evidence from studies with CBZ and PB in the rhesus monkey suggests that there is an increase both in the formation and elimination of CBZ-E with a larger induction in the activity of the hepatic monoxygenase(s) responsible for the conversion of CBZ to its epoxide (Patel *et al.*, 1981; Wedlund *et al.*, 1982). This is supported by the known inductive effect of PB on epoxide hydrolase (Bresnick *et al.*, 1977), which is assumed to be the major enzyme responsible for conversion of the epoxide to its transdihydradiol (Bertilsson, 1978). Higher urinary CBZ-trans-diol excretion has been reported in

patients taking CBZ in combination with DPH, PB or PRIM (Eichelbaum *et al.*, 1979).

Induction of the epoxide-diol pathway is unlikely to explain the findings in the VPA treated patients. VPA has been shown to inhibit the metabolism of DPH and PB (Levy & Koch, 1982) and a similar inhibitory process on the further metabolism of CBZ-EP may explain the higher CBZ-E/CBZ ratios in these patients. In the 15 patients on CBZ monotherapy there was a concentration-dependent increase in CBZ-E/CBZ ratios. CBZ is known to induce its own metabolism in a dose-dependent manner (Rapeport *et al.*, 1983). These data also suggest that CBZ-E formation is also induced and this is supported by studies of urinary metabolite excretion (Eichelbaum *et al.*, 1982).

A wide therapeutic range for CBZ of 4–10 mg l^{-1} has been quoted and the indications for monitoring CBZ in plasma is less clear cut than that for phenytoin (Perucca & Richens, 1981). This may well be due, in part at least, to the wide interindividual variation in steady-state CBZ-E concentrations. As CBZ is 75% protein bound in the plasma whereas CBZ-E binding is only 50% (MacKichen *et al.*, 1981), CBZ-E CSF concentrations may reach up to 50% of that of the parent compound (Morselli *et al.*, 1977). CBZ-E concentrations will undoubtedly be higher in these patients taking CBZ in high dosage or in combination with one or more other major anticonvulsant. These data are only clinically relevant if CBZ-E can be shown to possess equipotent anticonvulsant properties in man as it does in some rodent species (Frigerio & Morselli, 1975; Morselli *et al.*, 1975). CBZ-E kinetics in normal man have recently been reported (Tomson *et al.*, 1983). If its anticonvulsant properties are confirmed in epileptic patients, CBZ-E concentrations will provide a necessary additional refinement in the therapeutic drug monitoring of CBZ.

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