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Autoinduction and steady-state pharmacokinetics of carbamazepine and its major metabolites

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1 The effect of carbamazepine (CBZ) dose change on mean plasma concentrations of CBZ, its two metabolites and apparent steady-state clearance was studied in 77 affectively ill patients receiving CBZ at doses of 100–1200 mg day^{-1}.

2 Autoinduction of CBZ metabolism appeared to be complete within 1 week of starting CBZ therapy or dose change, and its degree was linearly related to CBZ daily dose.

3 Curvilinear plots were obtained for steady-state concentrations of CBZ and its -10, 11-epoxide metabolite, and for the ratio of CBZ-10,11-epoxide to CBZ level, versus daily dose of CBZ.

4 On the contrary, steady-state concentration of CBZ-10,11-diol increased proportionately with the dose. This indicates that there is no dose dependency in absorption of CBZ, and that dose-dependent autoinduction of CBZ metabolism is the main cause of the curvilinear relationship between dose and steady-state concentration of CBZ and its intermediary metabolite, CBZ-10,11-epoxide.

Keywords carbamazepine carbamazepine-10, 11-epoxide carbamazepine-10,11-diol steady-state pharmacokinetics autoinduction

Introduction

Carbamazepine (CBZ) has been used widely in the treatment of epilepsy and trigeminal neuralgia. In the mid-1970s the use of this drug in the treatment of affective disorders was introduced. CBZ kinetics have been extensively studied and reviewed (Levy & Kerr, 1988; Tomson *et al.*, 1989). However, no systematic data concerning CBZ steady-state pharmacokinetics have been reported.

Several metabolic pathways have been described and the cytochrome P450-mediated formation of CBZ-10, 11-epoxide (Figure 1) is the most important pathway of CBZ metabolism. CBZ-10,11-epoxide is almost entirely converted to CBZ-10,11-diol, which is excreted into urine in a free or conjugated form (Tomson *et al.*, 1983). CBZ-10,11-epoxide is an active metabolite, whereas CBZ-10,11-diol is inactive (Faigle & Feldmann, 1982; Tomson & Bertilsson, 1984).

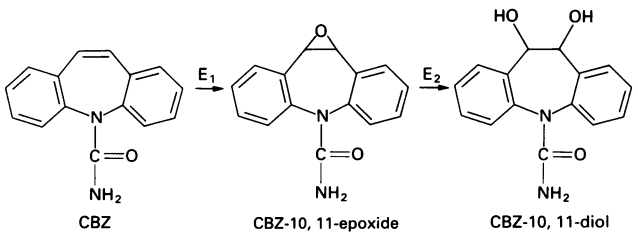

Figure 1 The epoxide-diol pathway of CBZ metabolism. E_1-monooxygenase, E_2-epoxide hydrolase.

Data concerning the relationship between plasma levels and daily dose of CBZ are incomplete and contradictory in the case of monotherapy as well as polytherapy. Some authors did not find any correlation (Nolen *et al.*, 1988), while others observed a linear relationship between the dose and plasma concentration of CBZ (Perucca *et al.*, 1980). As shown in some population (Battino *et al.*, 1980) or within-patient studies (Tomson *et al.*, 1989) at high doses, CBZ dose increase yielded a disproportionately small rise in CBZ plasma concentration. Numerous publications indicated that plots of steady-state concentration *vs* dose might be curvilinear and that this was probably due to the induction by CBZ of its own metabolism (Cloyd *et al.*, 1986; Levy & Kerr, 1988). Nevertheless, the character of the relationship between daily dose and plasma concentration of CBZ for therapeutic ranges of CBZ dose has not been clarified. This was the first objective of this study.

Autoinduction of CBZ metabolism is a time-dependent process. A majority of authors have reported that it occurs within the first month of CBZ therapy (Browne *et al.*, 1987; Levy & Kerr, 1988). A second objective of this investigation was to obtain more precise information concerning the time-dependency of autoinduction.

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In general, a poor relationship between dose and steady-state level of CBZ may be caused by several factors. The first one is high interindividual variability in CBZ concentrations in patients receiving the same daily dose. To overcome the influence of this factor mean population values for every dose were used in our study. Two other possible reasons are a dose-dependent autoinduction of the metabolism and reduced absorption of the drug at high doses. Determination of the CBZ metabolites is one way to elucidate this question.

Thus, the objectives of the present investigation were to characterize the time- and dose-dependency of CBZ autoinduction. With this aim the relationships of the apparent steady-state clearance of CBZ (the index of elimination rate) and the levels of CBZ and its two metabolites to daily dose of CBZ were studied.

Methods

Subjects

Steady-state pharmacokinetics were studied in 77 affectively ill patients (10 males and 67 females aged 19 to 60 years) treated prophylactically with CBZ (Finlepsin, Germed, DDR). The patients received CBZ at doses of 100–1200 mg/day. The treatment was performed with CBZ alone or in combination with neuroleptics, antidepressants, and tranquilizers. The patients were not on any other known inducers of hepatic metabolism. Twenty-one subjects (group 1) were studied from the beginning of CBZ therapy, whereas 56 subjects (group 2) had been receiving CBZ for at least 1 year prior to investigation. CBZ was administered 2 or 3 times a day at 09.30 h, 14.00 h, and 21.00 h or at 09.30 h and 21.00 h. The dosage schedules were individualized as deemed necessary by the treating physician. The establishment of the dose was according to clinical criteria. Drug administration was started with a daily dose of 100 mg and increased by 100 or 200 mg every 5–7 days until optimal efficacy was obtained without significant side effects. The maintenance prophylactic doses were in general achieved within the first month of the therapy. In some cases the dosages were readjusted during investigation because of insufficient efficacy or side-effects. Blood sampling was performed before the dose change during the first month of CBZ therapy and then monthly for a further 2 years. At 09.00 h prior to the morning dose of CBZ blood samples were taken to determine the levels of CBZ and its two metabolites. Measurements obtained for each patient at the same dose were averaged. The study protocol was approved by the Institute Ethics Committee, and verbal consent was obtained from all patients.

Measurements and calculations

Plasma concentrations of CBZ, CBZ-10,11-epoxide and CBZ-10,11-diol were analysed by high-performance liquid chromatography. A plasma sample of 100 μl was mixed with 20 μl of internal standard solution (nitrazepam, 20 μg ml^{-1}) and 100 μl of saturated solution of ammonium sulphate. Diethyl ether-dichlormethane mixture (2:1) was added (2 ml) and shaken for 10 min. After centrifugation (3,000 *g* for 3 min) the organic phase was transferred to a clean centrifuge tube and evaporated to dryness (40° C). The residue was dissolved in 20 μl methanol. The injection volume was 6 μl. A 64 × 2 mm column containing 5 μm Separon C-18 was equilibrated with 30% acetonitrile. Samples were eluted using a time gradient program: min 0, 30% acetonitrile; min 2, 40% acetonitrile; min 12, stop. The mobile phase flow rate was 100 μl min^{-1}. Ultraviolet detection was at 210 nm. Retention times were 3.61 min for CBZ-10,11-diol, 6.12 min for CBZ-10,11-epoxide, 8.90 min for CBZ, and 11.85 min for the internal standard. Quantification was achieved by reference of analyte/internal standard peak height ratios to suitable calibration curves. The sensitivity of the method was 0.13 μmol l^{-1} for CBZ, 0.11 μmol l^{-1} for CBZ-10,11-diol, and 0.08 μmol l^{-1} for CBZ-10,11-epoxide. The interassay coefficient of variation for each substance was less than 4% ($n = 6$) at levels relevant to the present investigation.

An estimate of the apparent steady-state clearance (ml min^{-1}) was obtained by

$$\hat{C}L_{ss} = \frac{D/T}{C_{ss}} \quad (1)$$

where D is daily dose of CBZ (mg), T is the dosing interval (1440 min), and C_{ss} – the steady-state trough concentration (mg ml^{-1}).

Comparison of the clearances was performed by Student's *t*-test. Correlations were evaluated by linear regression analysis. Fitted curves were obtained by least squares hyperbolic approximation.

Results

Table 1 shows a comparison of apparent steady-state clearances found at equal CBZ doses in patients during the first month of prophylactic treatment with CBZ and in those who had been taking this drug for not less than 1 year. There were no statistically significant differences in CBZ clearance at any of the doses studied. As the clearances were measured 5–7 days after beginning CBZ monotherapy or increasing the daily dosage it may be concluded that steady state (including the autoinduction) is achieved within a week of beginning CBZ intake or dosage change.

The relationship between dose and mean apparent

Table 1 Steady-state clearance of CBZ at different doses. Values are expressed as means ± s.e. mean

CBZ dose (mg day^{-1})	Clearance (ml min^{-1})			
	Group 1	n	*Group 2*	n
200	30.0 ± 2.4	14	34.5 ± 4.7	7
400	51.8 ± 9.8	11	48.0 ± 3.7	10
500	54.6 ± 2.5	7	57.1 ± 7.6	8
600	71.1 ± 7.7	16	75.9 ± 5.3	19

Group 1 – patients in whom the apparent steady-state clearance ($\hat{C}L_{ss}$) was assessed within the first month of CBZ treatment, 5–7 days after starting therapy or increasing the daily dosage; group 2 – those who had been receiving the same dosages for at least 1 year prior to investigation.

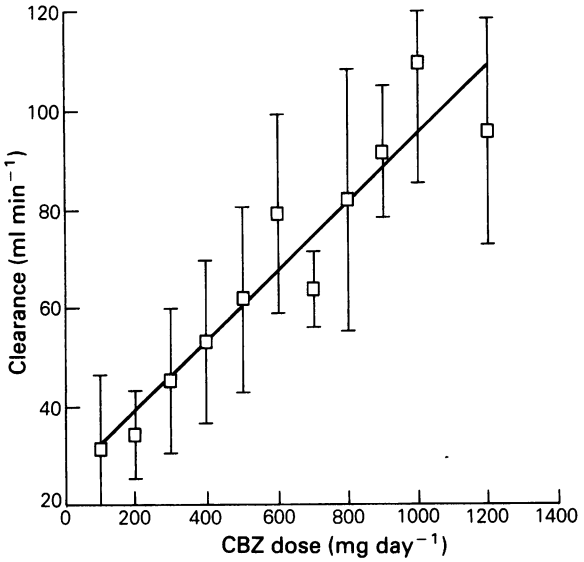

Figure 2 Relationship between dose and mean apparent steady-state clearance of CBZ. The bars indicate s.d.

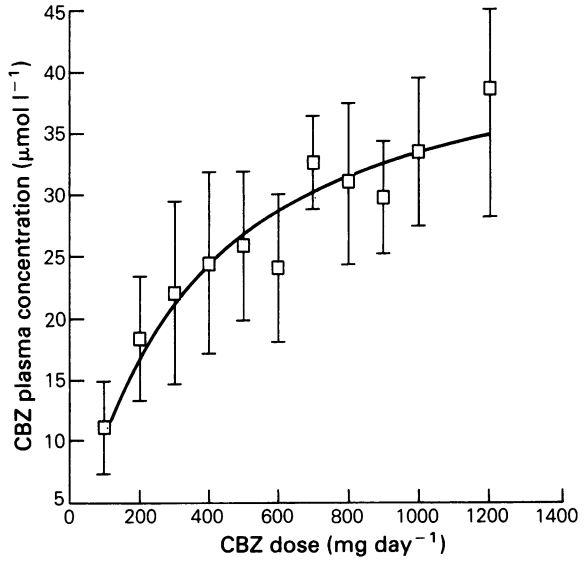

Figure 3 Relationship between dose and mean steady-state concentration of CBZ. Results are expressed as mean ± s.d.

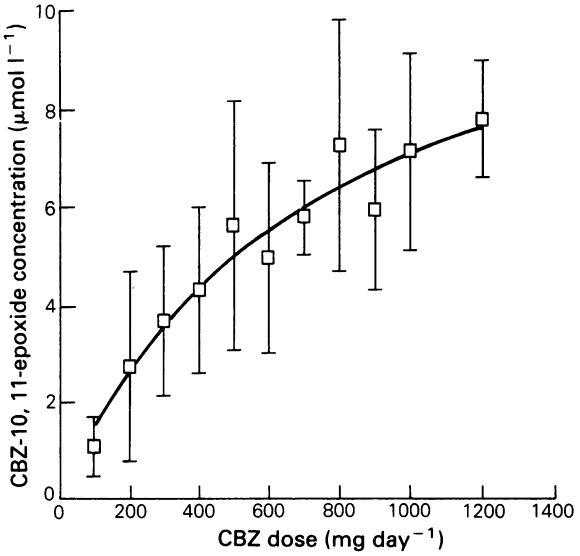

Figure 4 Relationship between CBZ dose and mean steady-state concentration of CBZ-10,11-epoxide. Results are expressed as mean ± s.d.

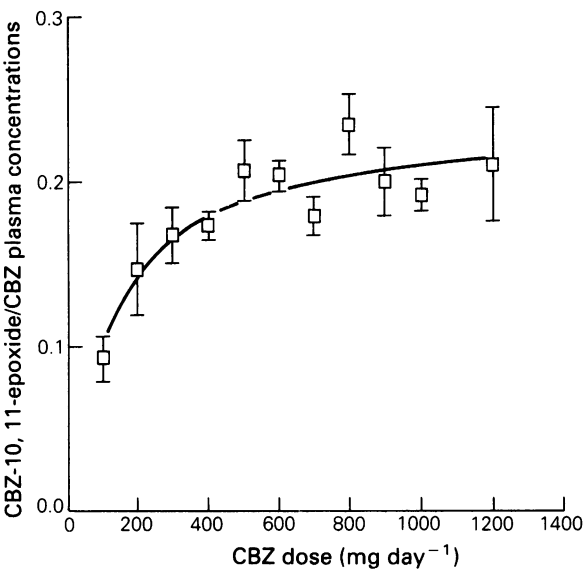

Figure 5 Relationship between CBZ dose and CBZ-10,11-epoxide/CBZ concentration (mean ± s.e. mean).

steady-state clearance of CBZ for 77 patients is shown in Figure 2. For oral doses from 100 to 1200 mg day^{-1} steady-state clearance varied between 31 and 110 ml min^{-1} and increased linearly with increasing CBZ dose ($r = 0.95$, $P < 0.01$). The linear regression equation for the clearance was

$$\hat{C}L_{ss} = 25.2 + 0.07D \quad (2)$$

The relationship of CBZ steady-state concentration (μmol l^{-1}) to dose was found from Equation 1 and 2:

$$C_{ss} = \frac{42.1\,D}{360 + D} \quad (3)$$

The latter is the equation of an hyperbola. The curve reflecting this equation is presented in Figure 3.

The plot of plasma steady-state CBZ-10,11-epoxide level versus dose was found to be nonlinear too (Figure 4).

Figure 5 shows the CBZ-10,11-epoxide/CBZ ratio as a function of CBZ dose. The ratio ranged from 0.09 ± 0.02 at 100 mg day^{-1} to 0.21 ± 0.06 at 1200 mg day^{-1} and depended more strongly on CBZ dose at low dosages.

The relationship between CBZ dose and mean plasma concentration of CBZ-10,11-diol is shown in Figure 6. The coefficient of correlation obtained for the 11 dose-level pairs was 0.993 ($P < 0.01$). Moreover, the regression line extrapolated to the Y-axis intersected it near the origin, so this relationship might be considered as linear and proportional.

Discussion

The apparent steady-state clearance assessed by Equation 1 was overestimated as concentrations lower than the average during a dosage interval were taken to calculate the clearance. Time steady-state clearance is, however, difficult to obtain as a frequent drug analysis within a dosing interval is required. Since all other things

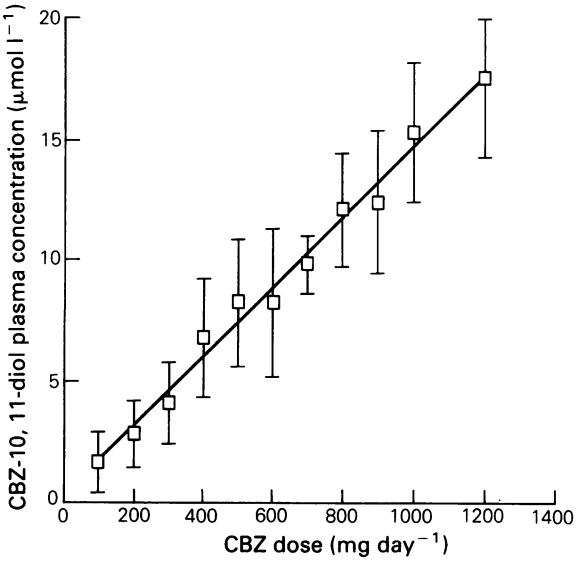

Figure 6 Relationship between CBZ dose and mean steady-state concentration of CBZ-10,11-diol. The bars indicate s.d.

were equal the estimate obtained can be used in comparative studies equally well to that normally calculated.

The present results corroborate the data of Browne *et al.* (1987) that autoinduction reaches its maximum during the first week of CBZ therapy. Our findings indicate that this is also true in the case of dosage change irrespective of the duration of CBZ therapy. In some patients whose dosages during therapy were reduced because of side-effects the clearances also quickly decreased, reaching their initial values. These results are in an agreement with those of Bertilsson *et al.* (1986) who found that the autoinduction was complete after the first few doses and disappeared with at same rate after CBZ discontinuation.

As seen in Table 1 apparent CBZ clearance tends to rise with the dose in equal measure in both naive subjects and those who have been receiving this drug for a long time. Figure 2 shows the linear relationship between the apparent CBZ steady-state clearance and daily dose for the whole therapeutic range of 100–1200 mg day^{-1}. These data suggest that there is a dose-dependent autoinduction of CBZ metabolism and that the apparent steady-state clearance can be used as a measure of the autoinduction.

The regression line extrapolated to the Y-axis yielded a mean clearance value similar to that obtained from single-dose kinetics (Tomson *et al.*, 1983): 25.2 *vs* 24.4 ml min^{-1}, respectively. These values evidently reflect uninduced baseline CBZ clearance.

The linear plot of steady-state clearance versus dose of CBZ obtained allowed the function approximating the relationship between CBZ dose and concentration to be calculated. As seen in Figure 3, at low doses (up to 500 mg day^{-1}) the relationship is nearly proportional. Further increase in CBZ dosage is accompanied by a small rise in steady-state CBZ concentration. A better correlation between dose and plasma level of CBZ at low doses was also observed by MacPhee & Brodie (1985). On the other hand, some authors have noted a disproportionately low increase in CBZ plasma concentration after a dose increase at high doses (Tomson *et al.*, 1989) or did not find a linear correlation throughout the therapeutic range (Nolen *et al.*, 1988; Post *et al.*, 1983). Thus, the plot of CBZ concentration *versus* dose found in the present study provides an explanation and shows that both these results are parts of the same curve.

The plots of steady-state concentration of CBZ-10, 11-epoxide *versus* CBZ daily dose, as well as of CBZ-10,11-epoxide/CBZ concentration ratio *versus* dose were found to be curvilinear too. Figure 5 shows that at low CBZ doses, from 100 to 500 mg day^{-1}, the ratio increases appreciably with the dose, whereas at the dose range between 500 and 1200 mg day^{-1} CBZ-10,11-epoxide/CBZ concentration ratio is nearly constant. There is a high degree of agreement between our results and those of Tomson *et al.* (1989). They found that over a CBZ dose range of 800–2000 mg day^{-1} the ratio calculated in the case of CBZ monotherapy was constant and varied interindividually between 0.15 and 0.29. A possible explanation of the curvilinear relationship between CBZ dose and its -10,11-epoxide metabolite level and between the dose and CBZ-10,11-epoxide/CBZ concentration ratio is that both the epoxidation of CBZ and the hydration of CBZ-10,11-epoxide are dose-dependent, but the induction of CBZ-10,11-epoxide hydration starts at higher CBZ doses than the epoxidation. The ratio CBZ-10,11-epoxide/CBZ in plasma in the case of monotherapy cannot be used therefore as an indicator of the degree of autoinduction of CBZ metabolism since the ratio depends on both rates of the epoxidation and the hydration. On the contrary, a higher CBZ-10,11-epoxide/CBZ ratio and lower steady-state CBZ concentration on polytherapy compared with monotherapy (Brodie *et al.*, 1983; Eichelbaum *et al.*, 1985) gives reason to suppose that CBZ metabolism inducers, in contrast to CBZ itself, influence mainly epoxidation and have much less effect on CBZ-10,11-epoxide hydration. In this case, the ratio could be used as an indicator of the degree of induction of CBZ phase one metabolism.

The relationship between CBZ-10,11-diol level and CBZ dose has not been previously studied. As shown by Tomson *et al.* (1983) CBZ-10,11-diol, the end metabolite of the epoxide-diol pathway, is eliminated by renal excretion and its elimination is not subject to enzyme induction. The proportionate relationship between CBZ daily dose and the -10,11-diol metabolite level found suggests that the systemic absorption of CBZ is not reduced at higher doses and that dose-dependent autoinduction of CBZ metabolism is the main cause of the curvilinear relationship between dose and steady-state concentration of CBZ and CBZ-10,11-epoxide.

Thus, this investigation confirms previous studies that there is curvilinear relationship between dose and steady-state concentration of CBZ and that this is due to the dose-dependent autoinduction of CBZ metabolism. Although the results were obtained using mean population values our preliminary investigations suggest that this is also true for individuals. Individual plots of the relationships appear similar, whereas the regression parameters differ.

Possibilities for the practical use of these relationships for the prediction of individual levels will be elucidated in further investigations. Another problem the present study highlights is the problem of prescribing high CBZ

doses, since a rise of both levels of pharmacologically active CBZ and its epoxide with a dose increase is rather small at high dosages and there is no convincing evidence of a clear relationship between the levels and clinical effects.

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