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STEADY STATE PHARMACOKINETICS OF CARBAMAZEPINE–PHENOBARBITAL INTERACTION IN PATIENTS WITH EPILEPSY

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ABSTRACT

Two carbamazepine (CBZ) tablet formulations (conventional, CBZ-CO, or controlled release, CBZ-CR) are commonly prescribed in monotherapy or in comedication with phenobarbital (PB) in the treatment of epilepsies. This study compares the pharmacokinetics of CBZ-CO against CBZ-CR in patients with epilepsies chronically treated with CBZ in monotherapy or CBZ-PB in bitherapy, the effect of PB on CBZ-CO and CBZ-CR pharmacokinetic parameters, and the effect of the two formulations of CBZ on PB pharmacokinetic parameters. The absorption rate constant (K_a), apparent steady state volume of distribution (V_{dss}/F), and apparent total clearance (CL/F) were computed with the APIS software using blood level profiles from 34 patients divided into four groups: patients receiving either CBZ-CO or CBZ-CR in monotherapy, or CBZ-CO or CBZ-CR in comedication with PB. The results show that the lowest dispersion of pharmacokinetic parameters was in patients receiving CBZ-CR in monotherapy. The CBZ formulation alters CBZ K_a, (V_{dss}/F) and (CL/F) values. CBZ (CL/F) also depends on the treatment (presence or absence of comedication by PB). In patients receiving PB in comedication with CBZ, the formulation of CBZ has no effect on PB pharmacokinetic parameters. These changes may be clinically significant and should be taken into account.

KEY WORDS: conventional carbamazepine; controlled-release carbamazepine; phenobarbital; pharmacokinetics; interaction

INTRODUCTION

Carbamazepine (CBZ), a major anticonvulsant drug, is commonly prescribed in monotherapy or in comedication with other antiepileptic drugs (AEDs) in the treatment of epilepsies. Conventional CBZ (CBZ-CO) is generally administered twice, three times, or four times daily, because of its relatively

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short half-life. Significant fluctuations of daytime CBZ plasma concentrations may be observed in patients on chronic CBZ therapy and side-effects may occur, particularly during the limited periods of maximal plasma concentration.[1,2]

During recent years, a new controlled-release formulation of CBZ (CBZ-CR) has permitted a reduced frequency of administration (usually b.i.d.). This has been reported to reduce the fluctuations of CBZ plasma concentrations.[3–7]

However, significant drug interactions may occur when other AEDs are coadministered with CBZ. The influence of the new CBZ-CR formulations on the pharmacokinetic parameters and that of drug interactions with other AEDs merit investigation. The purpose of this study was to compare the pharmacokinetics of CBZ-CO against CBZ-CR in patients with epilepsy chronically treated with CBZ in monotherapy or CBZ–phenobarbital (PB) in bitherapy, the effect of PB on CBZ-CO and CBZ-CR pharmacokinetic parameters, and the effect of the two formulations of CBZ on PB pharmacokinetic parameters.

MATERIALS AND METHODS

Patients

Thirty-four patients with epilepsy, free of clinical disorders which might affect pharmacokinetic parameters, were included in this study. Epilepsy was diagnosed according to the 1989 International Classification of Epilepsies and Epileptic Syndrome.[8]

The drug regimen had been stable for at least 2 months prior to study. Steady state conditions were validated after clinical and dosing monitoring. The patients received as monotherapy either CBZ-CO (Tegretol*, 200 mg tablets, Ciba–Geigy, Rueil Malmaison, France) or CBZ-CR (Tegretol* LP, 200 or 400 mg tablets, Ciba–Geigy, Rueil Malmaison, France), or CBZ-CO or CBZ-CR in comedication with PB (Gardénal*, 50 or 100 mg tablets, Rhône Poulenc-Rorer, France).

Seventeen patients were on CBZ monotherapy. Nine on t.i.d. dosing of CBZ-CO formed group 1 (age, 24 ± 12 years; body weight, 61 ± 16 kg; gender, four males (M), five females (F); dosage, $14{\cdot}4 \pm 5{\cdot}6$ mg kg^{-1} d^{-1}; epilepsy syndrome, nine symptomatic partial epilepsy (EPS)) and eight on b.i.d. dosing of CBZ-CR formed group 2 (age, 17 ± 8 years; body weight, 54 ± 19 kg; gender, 3 M, 5 F; dosage, $16{\cdot}9 \pm 5{\cdot}8$ mg kg^{-1} d^{-1}; epilepsy syndrome, four EPS, one cryptogenic generalized epilepsy (EGC), and three unclassified epilepsy).

Seventeen patients received CBZ-CO or CBZ-CR in association with PB. Nine on t.i.d. dosing of CBZ-CO formed group 3 (age, 25 ± 7 years; body weight, 56 ± 14 kg; gender, 2 M, 7 F; CBZ dosage, $18{\cdot}9 \pm 6{\cdot}5$ mg kg^{-1} d^{-1}, PB dosage, $2{\cdot}58 \pm 0{\cdot}74$ mg kg^{-1} d^{-1}; epilepsy syndrome, two EPS, one EGC, two

symptomatic generalized epilepsy (EGS), one cryptogenic partial epilepsy (EPC), and three unclassified epilepsy) and eight on b.i.d. dosing of CBZ-CR formed group 4 (age, 25 ± 9 years; body weight, 62 ± 19 kg; gender, 3 M, 5 F; CBZ dosage, 16·9 ± 5·5 mg kg^{-1} d^{-1}, PB dosage, 1·80 ± 0·54 mg kg^{-1} d^{-1}; epilepsy syndrome, three EPS, four EPC, and one unclassified epilepsy).

Methods

Six to eight blood samples were collected through a heparinized indwelling catheter during the 24 h sampling interval. The sampling protocol was not the same for all subjects; we suggested sampling once before the morning dose (t_0) and then, without stopping therapy, twice or three times between 2 and 6 h, twice or three times between 10 and 12 h, and once between 20 and 24 h after the morning dose. CBZ and PB total plasma levels were assessed by gas–liquid chromatography (GLC) according to Rovei *et al.*[9] by using the column methylation technique with trimethylphenylammonium hydroxide. Plasma CBZ and PB were extracted in a phosphate buffer with chloroform; imipramine was the internal standard. GLC analysis was performed on a Hewlett–Packard 5880 chromatograph equipped with a nitrogen–phosphorus selective detector (Hewlett–Packard Co., Palo Alto, CA, U.S.A). The GLC glass column (5 ft, 4 mm I.D.) was packed with 3% OV 17 on chromosorb w 80–100 mesh. The oven, injector and detector temperatures were 230, 300, and 300 °C, respectively. The carrier gas (nitrogen) flow rate was 50 mL min^{-1}. The limits of detection of the assay allow for quantification of at least 0·1 μg mL^{-1} of both drugs with 1 mL of sample. The coefficient of variation for quality control standards was less than 5% for both drugs.

We obtained 34 CBZ and 17 PB profiles with a total of 254 and 132 assayed concentrations respectively.

Pharmacokinetic analysis

Compartmental modelling was undertaken to assess CBZ and PB pharmacokinetics. The time–concentration courses were adequately described by a one-compartment model with the APIS software.[10,11] Because the parenteral forms were not available, bioavailability F was unknown and only apparent pharmacokinetic parameters could be computed: apparent steady state volume of distribution V_{dss}/F and apparent total clearance CL/F. These two parameters and the absorption rate constant K_a were analysed for the two formulations of CBZ, and for PB.

The diurnal fluctuations of plasma CBZ and PB concentrations were calculated for each patient as the difference between maximum and minimum concentrations as a percentage of the mean.[7] Maximum, minimum, and mean concentrations were computed by using the estimated model parameters.

Statistical analysis

Pharmacokinetic parameters were computed for the 34 patients divided into four groups, each with a homogeneous treatment regimen.

To assess the significance of K_a, V_{dss}/F and CL/F for CBZ between groups, the four groups were compared using two-way analysis of variance (ANOVA) with the 7D program of the BMDP Software (BMDP, Statistical Software Inc., Cork, Ireland). For PB comparisons, the Mann–Whitney test was applied using the 3D program of the same software. The null hypotheses tested were that the treatment (monotherapy or bitherapy) and formulation of CBZ (CO or CR) have no influence in the parameters studied for the four groups.

Outliers in the data set may have a marked effect on ANOVA tests. One extremely high value can inflate both the sample mean and standard deviation. This was the case for two patients with high K_a values in group 1 and for one patient with high V_{dss}/F and CL/F values in group 4. These three patients were not included in the statistical analysis because they might have induced an incorrect rejection of the null hypothesis or a failure to find significance when there is an effect.

A basic assumption underlying the ANOVA is equality of variances. If this assumption does not hold, the standard ANOVA does not provide a valid test of the equality of group means. We thus used the Brown–Forsythe[12] alternate test, in which the group variances are not assumed to be equal. For all these tests the significance level was fixed at 0·05.

Before performing ANOVA, we performed a principal component analysis to show the interindividual variability graphically, using the 4M program of the BMDP Software. This analysis was done to study the correlations among K_a, V_{dss}/F, and CL/F by clustering the variables into factors (such that variables within each factor are highly correlated) and locating the relative position of the four groups.

In general, principal component analysis is a useful tool in exploratory data analysis when one wants a parsimonious description for a set of continuous, intercorrelated variables. While accounting for most of the initial information within the data, the number of factors extracted is appreciably less than the original number of variables. Then, one could check for (1) recording errors or outliers, (2) anomalies in the statistical distributions, and (3) variables that are independent of the others and need not be included.

RESULTS

Figure 1 shows the fitting of the one-compartment model from the CBZ data in a patient receiving b.i.d. CBZ-CR in monotherapy. The adequacy of the model prediction is expressed by the coefficient of variation (CV) of the residual error. This CV varied between 4·55% and 26·90% among profiles.

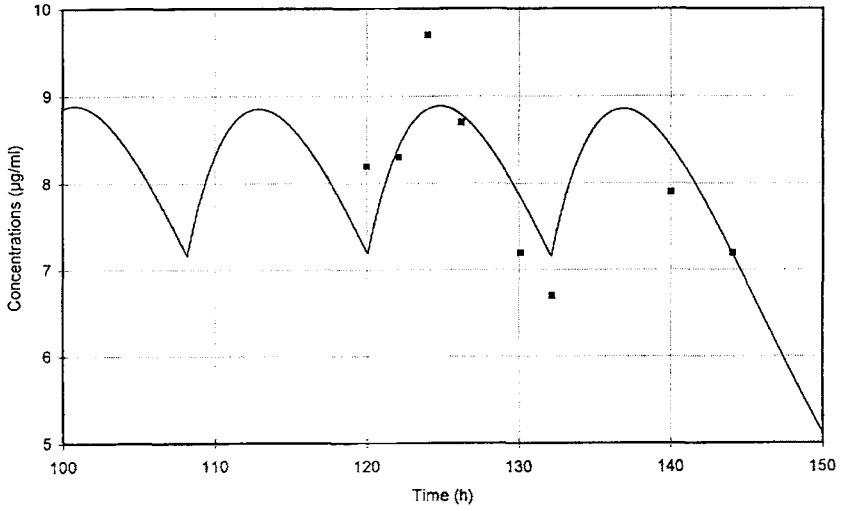

Figure 1. A typical fitting of the identified model to the data obtained at the steady state in a patient receiving b.i.d. CBZ-CR in monotherapy: ■ observed CBZ concentrations

Tables 1 and 2 express the mean values (m), standard deviations (s.d.) and associated CV of K_a,V_{dss}/F, and CL/F for CBZ and PB respectively. Table 3 shows the m and s.d. of diurnal fluctuations in plasma for CBZ and PB concentrations. Table 4 shows the p-values of the ANOVA test adjusted according to the Brown–Forsythe suggestion for K_a,V_{dss}/F, and CL/F of

Table 1. Mean parameter values of CBZ and dispersion in patients receiving CBZ-CO or CBZ-CR on monotherapy or bitherapy: K_a, absorption rate constant (h^{-1}); V_{dss}/F, apparent steady state volume of distribution (L); CL/F, apparent total clearance ($L\,h^{-1}$); n, number of patients in each group; m, mean value; s.d., standard deviation; CV, coefficient of variation

		Conventional CBZ			Controlled-release CBZ		
		K_a	V_{dss}/F	CL/F	K_a	V_{dss}/F	CL/F
Groups 1 and 2 Monotherapy	n	7	9	9	8	8	8
	m	0·22	39·5	3·28	0·11	41·2	4·22
	s.d.	0·11	15·0	1·12	0·03	11·0	1·01
	CV (%)	51·1	37·9	34·1	28·3	26·8	23·7
Groups 3 and 4 Bitherapy	n	9	9	9	8	7	7
	m	0·19	34·5	5·10	0·10	68·5	6·52
	s.d.	0·06	15·6	1·18	0·05	23·4	2·08
	CV (%)	32·9	45·2	23·2	45·1	34·2	31·9

Table 2. Mean parameter values of PB and dispersion in patients receiving PB on bitherapy with CBZ-CO or CBZ-CR: K_a, absorption rate constant (h^{-1}); V_{dss}/F, apparent steady state volume of distribution (L); CL/F, apparent total clearance ($L\,h^{-1}$); n, number of patients in each group; m, mean value; s.d., standard deviation; CV, coefficient of variation

		K_a	V_{dss}/F	CL/F
Group 3				
Bitherapy with CBZ-CO	n	9	9	9
	m	0·056	5·33	0·26
	s.d.	0·017	3·30	0·10
	CV (%)	30·1	61·8	38·9
Group 4				
Bitherapy with CBZ-CR	n	8	7	7
	m	0·046	5·61	0·22
	s.d.	0·025	2·32	0·05
	CV (%)	54·7	41·4	25·6

Table 3. Mean values and dispersion of diurnal fluctuations (as percentages) for CBZ and PB concentrations in patients receiving CBZ-CO and CBZ-CR on monotherapy or bitherapy: n, number of patients in each group; m, mean value; s.d., standard deviation

		CBZ-CO	PB	CBZ-CR	PB
Monotherapy	n	9	—	8	—
	m	42·5	—	19·5	—
	s.d.	13·8	—	10·2	—
Bitherapy	n	9	9	8	8
	m	42·8	7·1	18·9	7·1
	s.d.	14·4	3·6	10·7	6·0

Table 4. A statistical comparison (p values) between groups of patients receiving CBZ-CO and CBZ-CR on monotherapy or bitherapy: K_a, absorption rate constant (h^{-1}); V_{dss}/F, apparent steady state volume of distribution (L); CL/F, apparent total clearance ($L\,h^{-1}$)

	K_a	V_{dss}/F	CL/F
Formulation	0.002	0.009	0.036
Treatment	0.536	0.089	0.001
Statistical interaction	0.619	0.017	0.676

CBZ-CO and CBZ-CR. These values test the equality of formulation, the equality of treatment, and the equality of statistical interaction between formulation and treatment.

DISCUSSION

The results obtained for the pharmacokinetic parameters in patients receiving CBZ-CO in monotherapy are in agreement with those reported in the literature.[1,13–15] Table 1 shows that the CVs of pharmacokinetic parameters varied according to the patient groups receiving CBZ monotherapies. Dispersion of parameters was higher among patients on CBZ-CO against those on CBZ-CR, which is why the Brown–Forsythe test was applied. The lowest dispersion found in patients receiving CBZ-CR in monotherapy was due to the absence of drug interaction and to the smoothing effect of the CBZ-CR on plasma level fluctuations.

Principal component analysis showed that the variations of V_{dss}/F and CL/F are strongly correlated ($r = 0{\cdot}858$) and that two factors are sufficient to express 95% of the interindividual dispersion of parameters. The first factor is expressed by V_{dss}/F and CL/F and the second by K_a. Figure 2 graphically interprets the results of Table 1 and places all patient parameters in the plane defined by these two factors. One can visualize the relative position of the

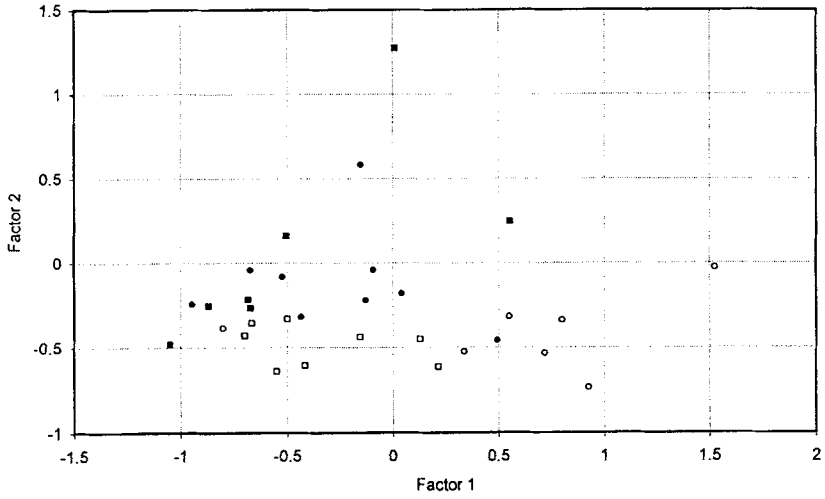

Figure 2. A plot of factor scores estimated by principal component analysis. Factor 1 represents CL/F and V_{dss}/F; factor 2 represents K_a. The relative position of groups 2 and 4 shows that PB induces an increase in CL/F and V_{dss}/F. The K_a values of patients on CBZ-CO (monotherapy and bitherapy) are higher than those of patients on CBZ-CR (monotherapy and bitherapy). ■, group 1, CBZ-CO in monotherapy; □, group 2, CBZ-CR in monotherapy; ●, group 3, CBZ-CO in bitherapy; ○, group 4, CBZ-CR in bitherapy

groups considered and draw conclusions about their dispersion. The position of group 2 with respect to group 4 (monotherapy against bitherapy in CBZ-CR) shows that PB induced an increase in V_{dss}/F and CL/F. This analysis shows that the second factor, expressed by K_a, discriminates between CO and CR formulations: the K_a values of patients on CBZ-CO are higher than those of patients on CBZ-CR.

Diurnal fluctuations (Table 3) in plasma CBZ concentrations confirmed the smoothing effect of the controlled-released form. Furthermore, PB fluctuations were lower than CBZ fluctuations (even for CBZ-CR) and were of the same extent for both CBZ formulations.

In Table 4, the results show that the following.

(1) the CBZ formulation alters CBZ K_a, V_{dss}/F, and CL/F values (p values respectively equal to 0·002, 0·009 and 0·036: the null hypotheses are rejected). The significant difference in the K_a values for CBZ-CO and CBZ-CR was expected because of the difference in CBZ formulations. In contrast, the differences found in the other parameters should be interpreted with caution. Indeed, it has been reported that the bioavailability of CBZ-CR, F_{CR}, is inferior to that of CBZ-CO, F_{CO}.[4,16–19] If the relation

$$\frac{CL_{CR}}{F_{CR}} > \frac{CL_{CO}}{F_{CO}}$$

is significant, the inequality may hold perhaps because $F_{CR} < F_{CO}$, without any relevant difference between CL_{CR} and CL_{CO}. The same remark holds for the significant difference detected for V_{dss}/F.

(2) CL/F also depends on the treatment (presence or absence of comedication by PB) (p value equal to 0·001: the null hypothesis is rejected). Then, it seems that PB induces an increase in CL/F in CBZ-CR and CBZ-CO patients probably because of the induction effect of PB.

(3) A significant statistical interaction between the CBZ formulation and the treatment was observed. The patient groups treated by CBZ-CR had significantly higher V_{dss}/F (p value equal to 0·017) than the other groups.

Lastly, the comparison of PB pharmacokinetic parameters between groups 3 and 4 did not show any significant difference (p values from the Mann–Whitney test equal to 0·10, 0·77 and 0·56 for K_a, V_{dss}/F, and CL/F respectively). It seems that the CBZ formulation does not interfere with PB pharmacokinetics.

It has been already shown that CBZ-CR both reduces the frequency of administration and smoothes the fluctuations of CBZ blood levels. Our results confirm these findings; the pharmacokinetic parameters were less dispersed in patients on CBZ-CR. It will be easier to adjust dosage with CBZ-CR than

with CBZ-CO. This may result in better control of seizures and reduction of dose-related side effects (dizziness, diplophia, nausea, headache, and light-headedness) sometimes observed with CBZ-CO during limited periods of peak plasma concentration. In patients receiving PB in comedication with CBZ, the formulation of CBZ has no effect on PB pharmacokinetic parameters. In such patients, the clinician should not worry about a change of PB pharmacokinetics when the formulation of coadministered CBZ is changed. However, PB generally induces a change of CBZ CL/*F* that leads to changes in plasma concentrations of CBZ: these changes may be clinically significant and should be taken into account.

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