A comparative pharmacokinetic study of conventional and chewable carbamazepine in epileptic patients

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Using an open substitution study design, conventional carbamazepine (Tegretol, CBZ-C) and a chewable carbamazepine formulation (Tegretol Chewtabs, CBZ-CHEW) were compared in 12 patients with severe intractable epilepsy. During a dosing interval, no significant differences were observed with respect to trough or peak serum concentrations of CBZ and CBZ-10,11-epoxide (CBZ-E), the active metabolite. The area under the serum CBZ concentration-time curve for a dosing interval was (mean $\pm$ s.e. mean) $146 \pm 10 \mu\text{mol l}^{-1} \text{ h}$ on CBZ-C and $143 \pm 9 \mu\text{mol l}^{-1} \text{ h}$ on CBZ-CHEW. The two formulations, therefore, have a similar pharmacokinetic profile and could be used interchangeably in the management of patients with epilepsy.

Keywords carbamazepine chewable carbamazepine pharmacokinetics bioavailability epileptic patients

Introduction

Carbamazepine (CBZ), a widely used anti-epileptic drug (AED), exhibits erratic absorption after oral ingestion with peak serum concentrations achieved within 2–8 h. Studies of various CBZ dosage formulations including suspensions, syrups, capsules and controlled release products have shown no difference in relative bioavailability (Larkin *et al.*, 1989; Loonen *et al.*, 1989; Morselli *et al.*, 1975; Pynnonen *et al.*, 1978). However, differences in absorption rate, peak serum drug concentrations and time to reach peak concentrations have been noted.

A chewable CBZ tablet (Tegretol Chewtabs), formulated for possible use by patients who have difficulty in swallowing and by children with epilepsy, has recently been shown in a series of 30 adult patients with epilepsy to be essentially equivalent to the conventional formulation in efficacy and tolerability (Patsalos *et al.*, 1990). The present paper describes and compares the steady state pharmacokinetics and relative bio-

availability of the two formulations in 12 of these patients. Further, the primary pharmacologically active metabolite of CBZ, carbamazepine-10, 11-epoxide (CBZ-E), which has been implicated in CBZ toxicity (Patsalos *et al.*, 1985) was also analysed.

Methods

Eight male and four female patients, with severe refractory epilepsy resident at the Chalfont Centre for Epilepsy took part in an open substitution study to compare the steady state pharmacokinetics of conventional (Tegretol, CBZ-C) and chewable (Tegretol Chewtabs, CBZ-CHEW) CBZ. The study design was approved by the Ethics Committee of the National Hospital for Nervous Diseases, London, and all patients gave informed consent.

Table 1 shows the main clinical details of the patients. All patients were on CBZ-C mainten-

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Table 1 Clinical details and pharmacokinetic parameters of patients

Patient	Age (years)	Sex	Duration of seizures (years)	Seizure type	Daily CBZ		CBZ serum concentration ($\mu\text{mol l}^{-1}$)				AUC ($\mu\text{mol l}^{-1} \text{ h}$)	
					dose (mg)	dose	CBZ-C $C_{\min}$	CBZ-C $C_{\max}$	CBZ-CHEW $C_{\min}$	CBZ-CHEW $C_{\max}$	CBZ-C	CBZ-CHEW
1	34	M	25	B,C	1800	26.1	35	44	28	37	156	130
2	35	M	25	B,C	1200	17.1	29	44	32	38	132	117
3	33	M	15	B,C	1400	17.5	31	52	29	38	161	129
4	38	M	12	D5	1200	16.0	20	25	24	32	92	118
5	30	F	18	B,C	1600	17.8	25	30	29	40	96	165
6	32	F	19	B	1600	26.2	55	60	42	53	198	190
7	36	M	27	D5	1600	20.2	31	35	27	29	127	104
8	34	M	27	A,C	1800	23.1	24	30	23	35	106	108
9	44	F	40	C	1400	18.9	36	41	39	42	171	165
10	38	F	30	A,C	1800	26.5	44	48	39	45	187	187
11	37	M	32	C	1600	23.2	27	36	25	41	182	171
12	28	M	21	A,C	1400	23.7	24	39	20	34	141	140
Mean							32	40	30	39	146	144
$\pm$ s.e. mean							± 3	± 3	± 2	± 2	± 10	± 9

A = Simple partial seizure; B = Complex partial seizure; C = Secondary generalized seizure; D 5 = Tonic-clonic seizure
 CBZ-C = conventional carbamazepine formulation; CBZ-CHEW = chewable carbamazepine formulation; AUC = area under the
 concentration-time curve; $C_{\min}$ and $C_{\max}$ = minimum and maximum concentrations.

ance therapy for at least 3 months prior to entering the study. Eight, three and one patient were respectively on two, three and four anti-epileptic drugs (AEDs). Concomitant AEDs included (number of patients): primidone (6), sodium valproate (5), phenytoin (3) and clobazam (3). Drug compliance was ensured during the study by tablet counting.

Patients routinely took their individualized CBZ-C medication at set times during the day (08.00, 13.00 and 20.00 h). Blood (10 ml) was withdrawn for the measurement of serum CBZ and CBZ-E concentrations at 0, 1, 2, 3, 4 and 5 h after the morning dose for 'dosage interval' analysis. CBZ-C was then substituted for an equivalent dose of CBZ-CHEW and 4 weeks later blood samples were taken at the same times as prior to substitution.

Measurement of serum CBZ and CBZ-E was by h.p.l.c. using the method of Elyas *et al.* (1986). Areas under concentration-time curves were calculated using the trapezoidal rule. Statistical analysis was performed using the Wilcoxon matched-pairs signed-ranks test for non-parametric data.

Results

Figure 1 shows the steady state serum concentrations of CBZ and CBZ-E during a dosing interval. No significant differences were observed with respect to trough ($C_{\min}$, time 0 h) or peak serum concentrations ($C_{\max}$, time 5 h; Table 1). The area under the serum CBZ concentration-time

Figure 1 Mean total serum drug concentration-time curves ($\pm$ s.e. mean) during a dosing interval (0–5 h) in 12 epileptic patients receiving conventional (●—●) and chewable (■—■) CBZ preparations. (CBZ, carbamazepine; CBZ-E, carbamazepine-10,11-epoxide).

curve for a dosage interval (AUC (0–5 h)) for CBZ-C and CBZ-CHEW were indistinguishable (Table 1).

The serum CBZ-E/CBZ ratio (means $\pm$ s.d.) for the two formulations was not significantly different. During a dosing interval the ratio was 0.33 ± 0.08 on CBZ-C and 0.35 ± 0.10 on CBZ-CHEW.

Protein binding was observed to be similar for both preparations. The percentage protein binding of CBZ and CBZ-E (mean $\pm$ s.d.) was, respectively, 77.1 ± 2.4 and 59.4 ± 4.7 on CBZ-C and 76.4 ± 3.3 and 57.6 ± 4.6 on CBZ-CHEW.

Substitution with CBZ-CHEW had no significant effects on the steady state serum concentrations of phenobarbitone (derived from primidone), valproic acid or phenytoin (data not shown).

Discussions

The pharmacokinetics and relative bioavailability of CBZ-C and CBZ-CHEW during chronic therapy in 12 patients with severe refractory epilepsy were compared. The results showed that the serum concentration-time profiles of CBZ-C and CBZ-CHEW are similar. The mean diurnal fluctuation of CBZ with CBZ-C was 25% and is in accordance with various previously reported estimates of 24–59% (Larkin *et al.*, 1989). The CBZ-CHEW preparation exhibited a mean diurnal fluctuation of 30% which was not significantly different from that seen with CBZ-C.

In a chronic dose study of healthy volunteers Chan *et al.* (1985) observed that the mean $C_{\max}$ of CBZ was 7% higher during CBZ-CHEW administration compared to CBZ-C. In the present study with epileptic patients we were unable to confirm those results. The difference may be attributed in part to the concomitant AEDs the patients were receiving and which are known to interact with CBZ.

The absence of any statistically significant difference in the AUC over a dosage interval at steady state suggests that the two formulations are bioequivalent and this was supported by comparable seizure rates during the two phases of treatment (data not shown). Interindividual variability for CBZ-CHEW was similar to that for CBZ-C so that monitoring of serum drug concentrations would be just as important for this formulation.

In conclusion therefore we have shown that Tegretol Chewtabs show a similar pharmacokinetic profile to that of the conventional formulation of Tegretol and that a significant change in steady state serum concentrations for most

patients is unlikely. Further, since the two formulations are therapeutically equivalent (Patsalos *et al.*, 1990) they could be used interchangeably.

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