Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients

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- 1 Fourteen patients with refractory epilepsy on a twice daily regimen of modified-release carbamazepine (CBZ-MR, Tegretol Retard, Ciba Pharmaceuticals) completed a balanced, double-blind, double dummy, random order, crossover comparison of 8 weeks treatment with once (o.d.) and twice daily (b.d.) dosing. In order to obtain a profile of serum CBZ concentrations over 24 h on once daily dosing, patients were randomised to taking it in the morning (o.d. a.m.) or evening (o.d. p.m.) for 4 weeks. Each treatment was taken with a placebo of the other and total tablet numbers were matched. Blood sampling was undertaken 0, 2, 4, 6, 8, 10, 12 and 24 h after the morning tablets at the end of each 4 week treatment period.
- 2 Overall, trough serum drug concentrations ($C_{\min}$) were lower with once daily dosing ($C_{\min}$: b.d. 7.5 mg l⁻¹, o.d. 6.5 mg l⁻¹, $P < 0.05$, 95% CI of the difference -1.3 to -0.1), but no significant differences were found in average (C_{av}) or peak ($C_{\max}$) concentrations, AUC values or fluctuations in CBZ concentrations.
- 3 Pharmacokinetic parameters for CBZ 10,11 epoxide, the active metabolite of CBZ, did not differ significantly between the dosage schedules.
- 4 Seizure control was similar during once and twice daily dosing with CBZ-MR (median seizures/month (range); b.d. 1 (0–14.5), o.d. 0.5 (0–11), NS, 95% CI of the difference -1.8 to $+0.25$).
- 5 There were no differences in psychomotor performance between the treatment periods.
- 6 More patients ($n = 11$) preferred treatment ($P < 0.05$) with once daily than twice daily dosing ($n = 3$) with CBZ-MR.
- 7 Once daily dosing with CBZ-MR should be possible in the majority of patients receiving the drug as monotherapy.

Keywords carbamazepine modified-release formulation clinical trial epilepsy

Introduction

Carbamazepine (CBZ) is a well-established treatment for partial and generalised tonic-clonic seizures [1]. The central nervous system side-effects associated with high peak serum CBZ concentrations can be offset by using a modified-release (MR) formulation [2]. This reduced the fluctuation in concentration during a dosage interval by around 50% in healthy volunteers [3]. In epileptic patients, less diurnal fluctuation in serum drug concentrations and minor improvements in psychomotor function were found with twice daily CBZ-MR compared with three and four daily dosing with conventional CBZ [4].

The current recommendation for CBZ-MR stipulates a twice daily dosage schedule. As this schema is also appropriate for conventional CBZ in many patients [5], only limited advantage is likely to accrue in clinical practice from prescribing the new formulation in this way. There is some evidence that once daily administration of CBZ-MR is possible [6]. We undertook a comparison of once against twice daily dosing of CBZ-MR in epileptic patients receiving the drug as monotherapy. Pharmacokinetic parameters were compared using a randomised, balanced, double-blind, double dummy technique.

Methods

Patients

Nineteen patients (12 women, seven men; aged 22–59 years) attending the epilepsy clinic at the Western Infirmary in Glasgow took part in a double-blind, double-dummy, random order, crossover comparison of once and twice daily dosing with CBZ-MR (Tegretol Retard, Ciba Pharmaceuticals) as monotherapy. Ten patients reported complex partial seizures, seven generalised tonic-clonic fits and two experienced simple partial seizures only. All had been established on CBZ-MR twice daily, the dose of which had not been altered during the previous 3 months. Seizure control was not optimal in these patients. None had clinical or biochemical evidence of hepatic, haematological or renal disease and all were requested to abstain from alcohol throughout the trial. The study was approved by the local ethics committee and all participants gave written informed consent.

Protocol

Patients continued to take CBZ-MR at their usual dose and timing for a 3 month baseline period, during which their seizures were charted on standard Western Infirmary seizure frequency forms. The patient was then randomised to receive once and twice daily (09.00 h and 21.00 h) CBZ-MR each for 8 weeks. During the once daily phase, CBZ-MR was taken as a morning (09.00 h) or evening (21.00 h) dose for 4 weeks in random order to obtain a 24 h serum drug concentration profile (Figure 1). A double-dummy technique was employed to control the study. Patients, therefore, received active CBZ once daily with twice daily placebo or active CBZ twice daily

with once daily placebo. To ensure blinding the treatment schedules were balanced, so that each patient took an identical number of tablets every day. Individualised dosing schedules were guaranteed by the use of Dosettes, which were provided for each patient by an unblinded pharmacist.

Patients attended the hospital following the baseline period and at the end of each 4 week treatment phase. At 09.00 h on each occasion, an indwelling catheter was inserted in a suitable antecubital vein and the morning tablets were administered. Two hourly blood sampling was undertaken over the next 12 h and a further sample was taken 12 h later just before the next morning dose for measurement of CBZ and its active metabolite, CBZ 10,11 epoxide (CBZ-E).

Seizure frequency charts were completed throughout the 16 weeks of the trial and compliance with medication was assessed at the end of each 4 week period by a tablet count. Psychomotor function tests, as previously described [7], were performed 1 and 4 h after the morning tablets on each study day to coincide with maximum serum CBZ concentrations [8]. On completion of the study and before the blind was broken, the patient gave his or her preference for one of the 4 months of treatment to one of the investigators (MJB), who was also unaware of the order of therapy.

Assays

Blood samples were allowed to clot prior to centrifugation and sera were stored at -20°C for batch analysis. CBZ was measured by enzyme immunoassay (Emit, Syva, Palo Alto, USA), while CBZ-E was determined by high performance liquid chromatography using 5-(*p*-methyl-phenyl)-5-phenyl hydantoin as internal standard [9]. Inter-assay coefficients of variation for

Figure 1 Study protocol for comparing once (o.d.) and twice (b.d.) daily dosing with modified-release carbamazepine (CBZ-MR) in a balanced, double-blind, double dummy manner in patients with refractory epilepsy taking the drug as monotherapy.

CBZ at 2, 8 and 12 mg l⁻¹ were 6.5, 4.7 and 3.4%, respectively. Corresponding values for CBZ-E at 0.5, 1.0 and 1.5 mg l⁻¹ were 4.0, 3.6 and 5.1%.

Pharmacokinetics

The trough ($C_{\min}$), peak ($C_{\max}$) and average (C_{av}) serum concentrations of CBZ and CBZ-E were calculated for each patient. AUC values were obtained using the linear trapezoidal rule. Results from once daily morning and evening administration of CBZ-MR were combined. Diurnal fluctuations in CBZ and CBZ-E concentrations were taken as the difference between maximum and minimum concentrations as a percentage of the mean [10].

Statistics

Statistical analyses of pharmacokinetic parameters and seizure frequencies were performed using the Wilcoxon matched pair and Mann Whitney U tests, respectively. Results of psychomotor tests were compared by analysis of variance and Student's *t*-test for paired samples with Bonferroni correction for multiple testing. Patient preference was assessed using the Chi squared test. Ninety-five percentage confidence intervals were calculated for the differences between medians of the pharmacokinetic and pharmacodynamic values. Assessment for a treatment period interaction was made by the method described by Hills & Armitage [11].

Results

Five of the 19 entered patients did not complete the study. Two did not comply correctly with the protocol and multiple venesections proved impossible in one patient. One woman was withdrawn for investigation of a bloody discharge from a nipple. A further patient withdrew before completion because of poor seizure control during treatment with single dose CBZ-MR in the evening. The median daily CBZ dose in the remaining 14 patients was 1100 mg (range 400–1400 mg).

There were no significant differences over 12 h in C_{av} , $C_{\min}$ and $C_{\max}$ values, and AUCs between the twice daily CBZ-MR treatment periods (data not shown). This suggested good compliance with medication, which was supported by the tablet counts at the end of each 4 week study period. Combining the data over 24 h (Figure 2), administration of CBZ-MR once daily produced significantly lower $C_{\min}$ values ($P < 0.05$, Table 1). No important differences, however, in $C_{\max}$, C_{av} and AUCs for CBZ were noted between once and twice daily dosing. As would be expected, the fluctuations in CBZ concentration were greater during once daily dosing, but not significantly so. C_{av} , $C_{\max}$ and $C_{\min}$, AUCs and fluctuations in CBZ-E concentrations did not differ between once and twice daily CBZ-MR dosing (Table 1).

Median (range) seizure frequencies per month were similar during once and twice daily dosing (o.d. 0.5 (0–11); b.d. 1.0 (0–14.5), 95% confidence intervals of the difference –1.8 to +0.25) and did not differ significantly from baseline values (0.85 (0–19)). There were no significant differences in cognitive function between once and twice daily dosing with CBZ-MR 1 and 4 h after ingestion of the morning tablets (Table 2). There was no evidence of a period effect for any of the data.

Figure 2 Median serum carbamazepine concentrations at each time point from pooled data of 14 epileptic patients receiving treatment with the same dose of modified-release carbamazepine given once (●) and twice (○) daily.

Table 1 Median pharmacokinetic parameters over 24 h in 14 epileptic patients treated with the same dose of modified-release carbamazepine given once and twice daily

	Twice daily	Once daily	P	95% confidence intervals of the difference
Carbamazepine				
$C_{\max}$ (mg l ⁻¹)	11.7	11.1	NS	–0.8 to +1.3
$C_{\min}$ (mg l ⁻¹)	7.5	6.5	<0.05	–1.3 to –0.1
C_{av} (mg l ⁻¹)	9.3	8.6	NS	–1.0 to +0.3
AUC (mg l ⁻¹ h)	226	211	NS	–12 to +20
Fluctuation (%)	35	40	NS	–6 to +24
Carbamazepine epoxide				
$C_{\max}$ (mg l ⁻¹)	1.5	1.4	NS	–0.2 to +0.1
$C_{\min}$ (mg l ⁻¹)	0.8	0.6	NS	–0.2 to +0.2
C_{av} (mg l ⁻¹)	1.2	0.9	NS	–0.2 to +0.1
AUC (mg l ⁻¹ h)	28.1	20.7	NS	–4.0 to +0.3
Fluctuation (%)	66	62	NS	–37 to +16

Table 2 Mean scores on cognitive testing 1 and 4 h after morning tablets in 14 epileptic patients treated with the same dose of modified-release carbamazepine taken once and twice daily

	1 h				4 h			
	Once daily (a.m.)	Once daily (p.m.)	Twice daily	Twice daily	Once daily (a.m.)	Once daily (p.m.)	Twice daily	Twice daily
Decision time (ms)*	0.49	0.47	0.48	0.53	0.46	0.49	0.50	0.52
Movement time (ms)*	0.30	0.42	0.30	0.42	0.29	0.28	0.28	0.28
Finger tapping (taps 15 s ⁻¹)	87.6	85.4	85.9	81.0	86.2	86.7	84.9	86.9
Forward digit span	6.5	6.4	6.4	6.6	6.9	6.6	6.6	7.0
Backward digit span	4.7	4.6	4.4	5.2	4.6	4.6	4.6	4.4
Paired learning*	14.1	14.4	13.6	12.9	11.1	11.4	11.3	12.1
Tracking test	14.8	15.2	13.0	18.3	14.8	17.6	14.6	17.1
Threshold detection	1.7	1.8	1.7	1.2	1.5	1.2	2.5	1.8
Side-effect score (cm)*	7.9	5.4	4.7	6.1	7.3	4.2	5.3	6.1
General health questionnaire	3.9	6.1	3.9	4.6	—	—	—	—
Sedation score (cm)*	2.0	3.1	2.7	2.3	2.6	1.7	3.2	2.0

*Tests in which a low score is better than a high score.

Eleven of the 14 patients preferred treatment with once daily CBZ-MR ($P < 0.05$). Six elected to take the total dose in the evening and five felt better with a morning dosage schedule. Two patients, however, complained of minor symptoms of headache and depression during the single dose CBZ-CR phase. Median (range) peak serum CBZ concentrations were significantly higher among patients during the once daily treatment phase who elected to remain on twice daily doses at the end of the study, compared with those who preferred once daily dosing (o.d.: $C_{\max}$ 10.7 (6.6–12.9) mg l⁻¹; b.d.: $C_{\max}$ 12.7 (11.5–15.8) mg l⁻¹, $P < 0.05$, 95% confidence intervals for the difference +0.1 to +7).

Discussion

Carbamazepine is a first-line anticonvulsant drug with established efficacy for the treatment of generalised tonic-clonic and partial seizures [1]. Its long elimination half-life of 30 h reduces with chronic administration to around 10 h [12, 13]. This is a consequence of auto-induction of metabolism, which is also responsible for substantial intra- and interindividual variation in circulating concentrations within a dosage interval [8]. High peak CBZ concentrations have been implicated in the production of the intermittent central nervous system symptoms (nausea, headache, diplopia, ataxia) associated with the drug [10, 14, 15]. This limits the maximum amount of CBZ that can be prescribed [5]. Dividing the dose further may improve the side-effect profile, but at the expense of compliance [16].

The modified-release formulation of CBZ was introduced as a means of reducing the daily fluctuation in serum drug concentrations and of simplifying the dosage regimen [17–21]. The patient may realise these kinetic benefits in fewer side-effects, improved compliance and better seizure control [2, 22]. Open [18, 23, 24], single-blind [19, 25] and double-blind studies in healthy volunteers and in epileptic patients [3, 4, 17, 20, 21, 26] have shown that twice daily administration of CBZ-MR has a pharmacokinetic profile and efficacy similar to three and four times daily dosing with conventional CBZ. Formal psychomotor testing using adequate

placebo controls also favoured CBZ-MR [4, 25].

Two open studies have explored the possible use of CBZ-MR as a single daily dose. In 48 epileptic patients, eleven of whom were previously untreated, CBZ-MR monotherapy was prescribed in the evening [6]. Thirty-five were monitored clinically for a mean duration of 1 year and 21 patients had serial measurements of CBZ concentrations made over 24 h for kinetic evaluation. Overall, 65% reported an improvement in seizure control; 80% felt comfortable on the single dose therapy and no patient noted a deterioration in fit frequency. In another single-blind crossover study in six patients, two modified-release preparations given once daily were compared with conventional CBZ [27]. Although primarily a kinetic study, no changes in seizure frequency or tolerability were noted. Only small differences in kinetic profile between the treatment schedules were shown.

This is the first double-blind study in which epileptic patients were treated with single daily doses of CBZ-MR. The patients were still experiencing seizures and so might be expected to experience some difficulty in changing dosing regimens. Despite this, changing to single daily dose proved uneventful in the majority.

The lower trough serum drug concentrations observed during once daily dosing in this study may, theoretically, result in a poorer seizure control in some patients. A non-significant decrease in CBZ trough concentrations was recorded when single dose CBZ-MR was compared with conventional CBZ taken three times daily [27]. In both open studies exploring the use of single doses of CBZ-CR, no increase in seizure numbers was recorded [6, 27]. In some patients, an improvement in seizure control was observed [6]. However, approximately seven percent of patients required to take CBZ-MR twice daily to achieve maximum benefit [6]. No significant difference in fit frequency was observed in our study. However, one patient was withdrawn because of increased seizures when taking CBZ-MR as a single dose in the evening. Failure to control seizures adequately with CBZ-MR once daily should result in changing to a twice daily regimen before abandoning the drug altogether.

Single dose CBZ-MR was well tolerated with minor complaints of headache and depression in just two

patients who completed the study. These symptoms may be attributable to the higher peak CBZ concentrations during once a day dosing as observed in the three patients who elected to remain on twice daily therapy. Rather surprisingly, 11 of 14 patients preferred once to twice daily dosing. This may simply be a reflection of the slightly lower CBZ concentrations.

In this small study, a single daily dose of CBZ-MR was well tolerated by the majority of patients. Kinetic differences between once and twice daily dosing were less than might be anticipated, perhaps because of reduction in the extent of autoinduction of metabolism

on a once daily schedule [8, 28]. The lower trough CBZ concentrations observed with this regimen, however, invite careful monitoring in patients who continue to experience seizures. Currently, we prescribe CBZ-MR once daily for patients with poor compliance who experience few seizures and in newly diagnosed patients, the majority of whom can expect complete seizure control with a modest dose of the drug.

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