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A double-blind comparison of conventional and controlled-release carbamazepine in healthy subjects

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1 Eight healthy subjects took part in a balanced, double-blind, crossover comparison of conventional carbamazepine (Tegretol, Ciba-Geigy Ltd, CBZ-C) and a novel controlled-release formulation (Tegretol CR Divitabs, Ciba-Geigy Ltd; CBZ-CR). An initial single dose of either preparation was followed 1 week later by a 2 week course of 200 mg twice daily.

2 Following the single dose, CBZ-CR produced a concentration plateau from 6–56 h at 50–60% of the CBZ-CR peak.

3 After 2 weeks' treatment, CBZ daytime levels measured as area under the concentration-time curve over a dosage interval were 7% lower with CBZ-CR, but this difference was not statistically significant.

4 CBZ-CR showed less diurnal fluctuation (12%) of CBZ than CBZ-C (24%; $P<0.025$) with less rapid changes in concentration ($P<0.02$).

5 Diurnal fluctuation of free CBZ and of CBZ 10,11 epoxide, the active metabolite, did not differ significantly between the two preparations.

6 Auto-induction of CBZ metabolism resulted from the administration of both formulations. The mean elimination half-life was 23 h (CBZ-C) and 25 h (CBZ-CR) after dose 29 compared with a base-line value of 37 h (both $P<0.02$). Antipyrine metabolism was also induced to a similar extent in both legs of the study ($P<0.01$).

7 No significant alteration in psychomotor function was demonstrated with either preparation.

8 CBZ-CR fulfils the criteria for a controlled-release preparation with comparable apparent bioavailability to CBZ-C. Further pharmacokinetic and, more importantly, pharmacodynamic studies are required in epileptic patients to confirm a clinical advantage over the currently available formulation.

Keywords carbamazepine controlled-release pharmacokinetics enzyme induction bioavailability

Introduction

All anticonvulsants have sedation as a major side-effect (Reynolds, 1983) and this can be measured to some extent by tests of psychomotor and cognitive function (Hindmarch, 1980; Brodie *et al.*, 1987). Carbamazepine (CBZ) has been suggested as being less sedative than the other first-line agents (Thompson & Trimble, 1982; Andrewes *et al.*, 1982) but it has been shown to impair psychomotor function both in healthy subjects (Macphee *et al.*, 1986a) and in patients on high dosage (Macphee *et al.*, 1986b). A sudden increase in concentration may be more

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important than the specific height of the level attained (Lesser *et al.*, 1984; Macphee *et al.*, 1986b). Large diurnal fluctuations of CBZ concentrations have also been found to correlate with intermittent side-effects (Hoppener *et al.*, 1980; Riva *et al.*, 1984; Tomson, 1984). This fluctuation occurs despite an initial half-life exceeding 24 h, since auto-induction of metabolism on chronic dosing lowers the half-life to approximately 12 h with monotherapy, and nearer 8 h in those taking more than one enzyme-inducing anticonvulsant (Eichelbaum *et al.*, 1983). A controlled-release preparation of CBZ may 'smooth' out this fluctuation and so be useful in diminishing side-effects, as well as possibly increasing the drug's potential for seizure control by permitting higher steady-state concentrations. Such a formulation might also be expected to improve compliance in patients currently receiving 3 or 4 daily doses.

The aim of the present study was to determine whether a new controlled-release formulation could be demonstrated to have a superior pharmacokinetic profile to that of conventional CBZ using a double-blind, crossover technique. The metabolite, CBZ 10,11-epoxide (CBZ-E), is known to have an anticonvulsant action (Frigerio & Morselli, 1975) and may also be implicated in CBZ toxicity (Patsalos *et al.*, 1985). Analyses of CBZ-E concentrations, together with the pharmacologically active free fraction of CBZ, were also undertaken.

Methods

Eight healthy volunteers (seven male, one female; ages 25–47 years) took part in a double-blind, balanced, crossover study of conventional (Tegretol, Ciba-Geigy Ltd, CBZ-C) and controlled-release (Tegretol CR Divitabs, Ciba-Geigy Ltd, CBZ-CR) CBZ. No subject had clinical or biochemical evidence of hepatic, haematological or renal disease. No concurrent medication was taken during the study. A minimum wash-out period of 1 month was considered adequate between the two legs, each of which lasted 3 weeks, as we have previously found enzyme induced effects to have abated 2 weeks after discontinuing the drug (Rapeport *et al.*, 1983). The study was approved by the local Ethics Committee and all subjects gave informed consent.

Single dose

Following a single 400 mg dose of CBZ-C or CBZ-CR, blood was drawn 0,2,4,6,8,10,14,24, 32,48 and 56 h later for measurement of circulating CBZ, free CBZ and CBZ-E concentrations. Psychomotor function tests were performed just prior to CBZ ingestion and 10 h later, equivalent to the expected time to peak concentration (Evans & Gaultieri, 1985). Baseline antipyrine kinetics were also assessed 48 h before CBZ ingestion, subjects taking 600 mg by mouth and supplying 5 ml samples of saliva for analysis after 0,3,5,8,12,24 and 32 h.

Chronic dosing

Subjects took 200 mg of the appropriate preparation at 09.00 h and 21.00 h daily for 2 weeks finishing with the 29th dose at 09.00 h on the 15th day. Tablet counting ensured compliance. Blood was withdrawn for the measurement of CBZ and CBZ-E concentrations after the first and fifteenth (eighth day) doses at 0,2,4,6,8,10 and 12 h for 'dosage interval' analysis and again after the 29th dose (15th day) at times similar to those employed in the single-dose phase.

Psychomotor function tests were performed on days 1, 8 and 15 of each leg of the study at 0,3,6 and 10 h after the morning dose. Antipyrine kinetics were repeated on the 8th and 15th days of CBZ administration.

Assays

Blood samples were centrifuged immediately after withdrawal and the serum was stored at −20° C for batch analysis. Total and free CBZ were assayed by equilibrium dialysis and enzyme immunoassay (EMIT, SYVA, Palo Alto) as described previously (Macphee *et al.*, 1986a), while CBZ-E was determined using a high performance liquid chromatographic (h.p.l.c.) method (Macphee *et al.*, 1984) with 5-(*p* methylphenyl)-5-phenyl hydantoin as internal standard. Antipyrine was measured using a modification of the h.p.l.c method of Shargel *et al.* (1979) as outlined previously (Macphee *et al.*, 1984).

Psychomotor tests

Psychomotor function tests included critical flicker fusion threshold (c.f.f.t.), choice reaction time (CRT), card sorting and finger tapping, as described previously (Macphee *et al.*, 1986a) together with digit span and a visual analogue scale (alertness score) of 'awakeness' or 'alertness' to give an all-round assessment of memory, sensory, motor and integrative function (Hindmarch, 1980).

C.f.f.t. was the frequency, measured while increasing (c.f.f.t.i.) or decreasing (c.f.f.t.d.), at

which a flickering diode is seen as a constant light. CRT was the time to respond to a flashing light and cancel a button (CRT_1 – time for initial response, CRT_2 – time for complete manoeuvre). Card sorting was of a conventional pack into aces, kings, etc., while finger tapping was performed on a calculator key with recording of number of taps achieved min^{-1}.

Kinetics and statistics

Antipyrine and CBZ kinetic parameters were obtained by linear regression using the method of least squares. Areas under the concentration-time curve were calculated using the trapezoidal rule. Statistics were performed with the Wilcoxon matched-pairs signed-ranks test for non-parametric data. Diurnal fluctuation was calculated as the difference between maximum and minimum concentrations expressed as a percentage of the mean (Riva *et al.*, 1984). Confidence intervals were calculated using Mann-Whitney confidence interval test on Minitabs Release 5.1.

Results

Pharmacokinetics

Following the single dose of CBZ-CR, CBZ concentrations plateaued around 60% of the peak obtained with CBZ-C (Figure 1). Steady-state concentrations were slightly lower with CBZ-CR at 29 days (Figures 2, 3) but this difference was not statistically significant with respect to trough or average concentrations. Free CBZ levels followed a similar pattern to total CBZ (Figure 4). The percentage protein binding was the same with both preparations, the mean (± s.d.) values at each time point after the 29th dose ranging from 73.9 ± 4.5% to 75.2 ± 2.4% on CBZ-C, and from 74.4 ± 2.7% to 75.7 ± 2% on CBZ-CR. CBZ-E levels on CBZ-CR were lower than on CBZ-C but not significantly so (Figure 5).

Bioavailability

The area under the concentration-time curve for a dosage interval (AUC 0–12 h) was calculated following the 15th and 29th doses (Figure 6). After the 15th dose mean results ± s.d. were CBZ-C 84 ± 17 mg l^{-1} h and CBZ-CR 85 ± 15 mg l^{-1} h (95% confidence intervals for the difference +16 to −20). After the 29th dose, the AUC values were CBZ-C 80 ± 16 mg l^{-1} h and CBZ-CR 75 ± 16 mg l^{-1} h (95% confidence interval for the difference +23 to −12).

Fluctuation

Diurnal fluctuation of CBZ concentrations around the mean at steady-state (Figure 7) was

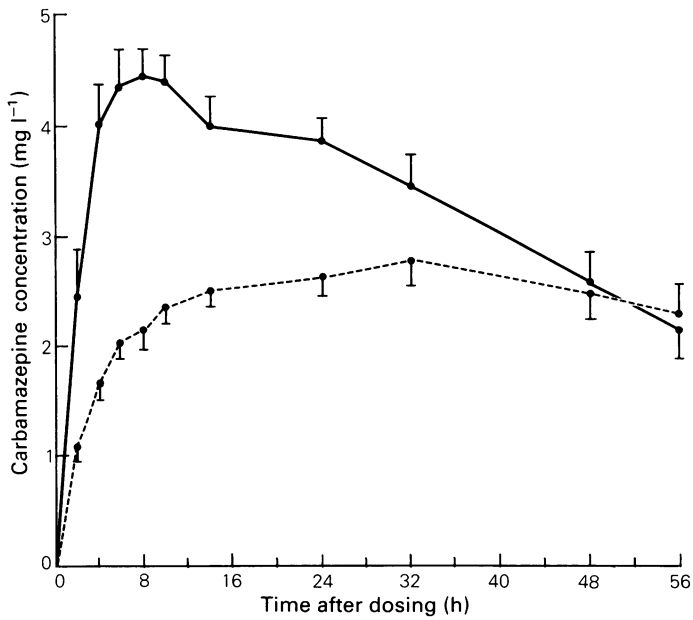

Figure 1 Mean plasma drug concentration-time curves (± s.e. mean) following a single 400 mg dose of carbamazepine in eight subjects receiving conventional (●—●) and controlled-release (●---●) preparations.

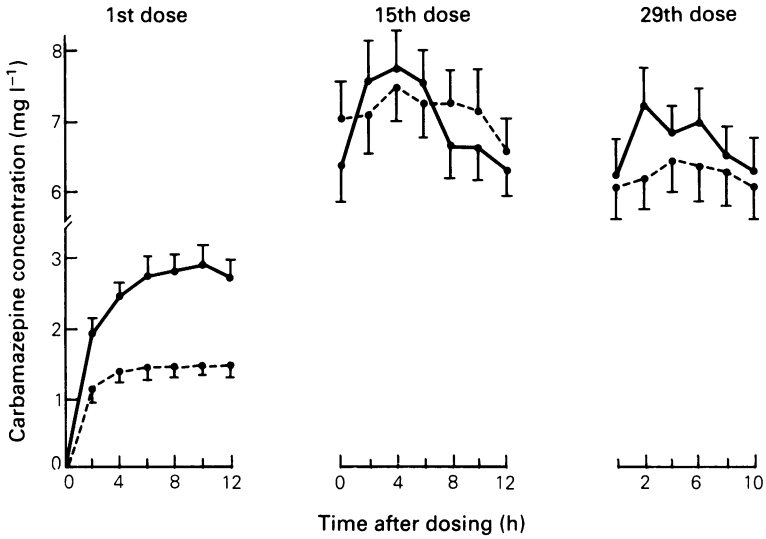

Figure 2 Mean diurnal plasma drug concentration time curves (± s.e. mean) in eight subjects after 1st, 15th and 29th dose of conventional (●—●) and controlled-release (●---●) carbamazepine.

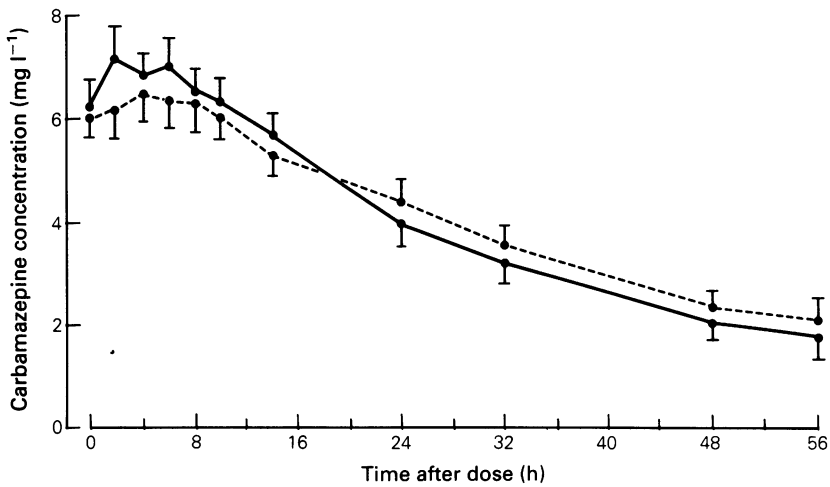

Figure 3 Mean plasma drug concentration-time curves (± s.e. mean) in eight subjects following the 29th dose of 14 day treatment schedules of 200 mg twice daily of conventional (●—●) and controlled-release (●---●) carbamazepine.

significantly less with CBZ-CR (12%) than with CBZ-C (24%, $P<0.025$, 95% confidence intervals for the difference + 4% to +18%). The maximum increase in concentration in any 2 h period is shown for each individual subject on CBZ-C and CBZ-CR in Figure 8. This was also lower with CBZ-CR ($P<0.02$). Decreased fluctuation of free CBZ and epoxide concentrations with CBZ-CR seemed possible from the data in Figures 4 and 5 where the standard error bars do not overlap during the 'peaking' of CBZ-C. However, although there was a consistent trend with both free CBZ and CBZ-E to show less fluctuation than with the other preparation, these differences did not reach conventional levels of significance.

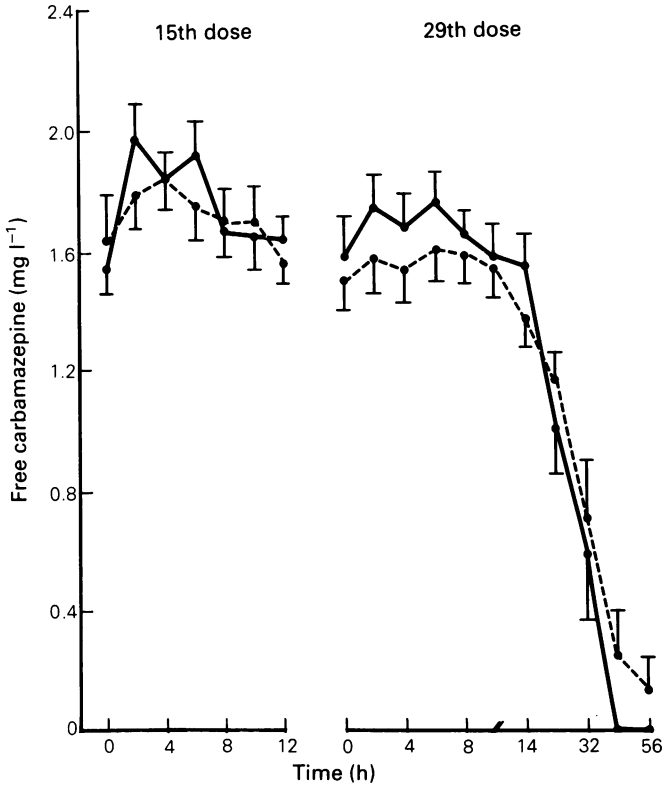

Figure 4 Mean diurnal plasma drug concentration-time curves (± s.e. mean) of free carbamazepine in eight subjects after 15th and 29th 200 mg dose of conventional (●—●) and controlled-release (●---●) carbamazepine.

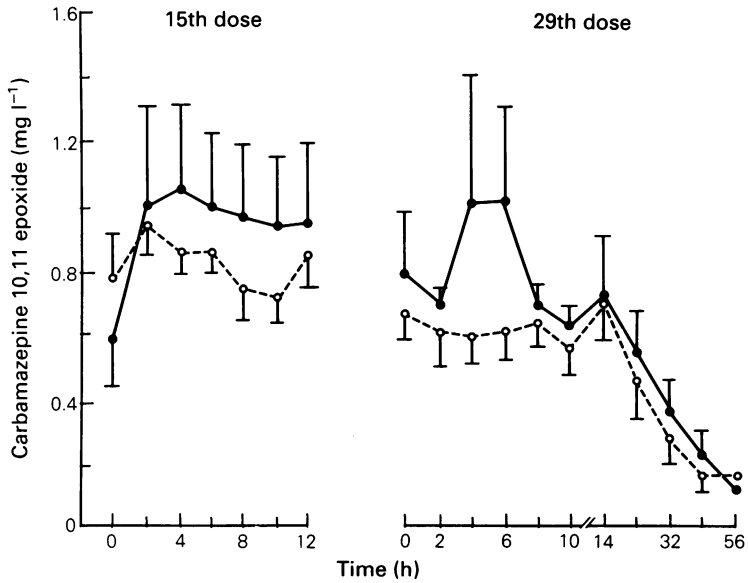

Figure 5 Mean diurnal concentration-time curves (± s.e. mean) of plasma carbamazepine 10,11 epoxide in eight subjects after 15th and 29th 200 mg dose of conventional (●——●) and controlled-release (○---○) carbamazepine.

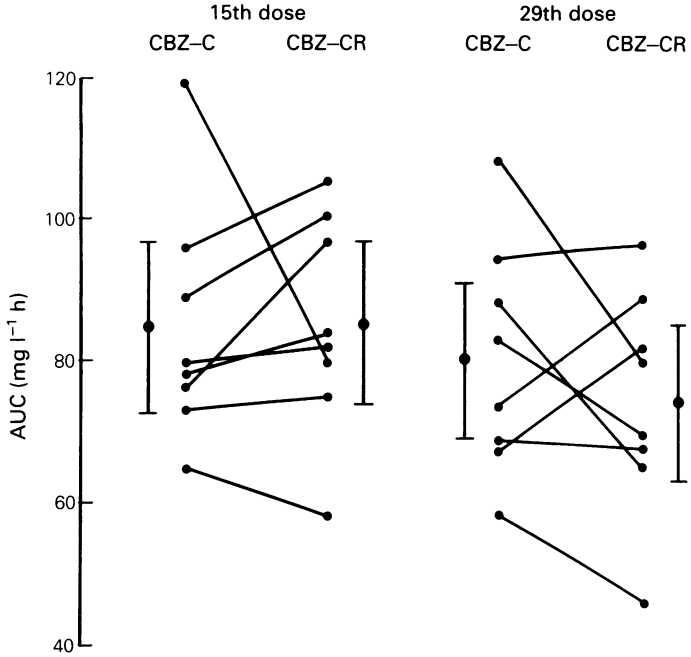

Figure 6 Areas under concentration-time curves (0–12 h) following 15th and 29th dose of 200 mg twice daily schedule of conventional carbamazepine (CBZ-C) and a controlled-release preparation (CBZ-CR) in eight subjects. Vertical bars represent mean ± s.e. mean.

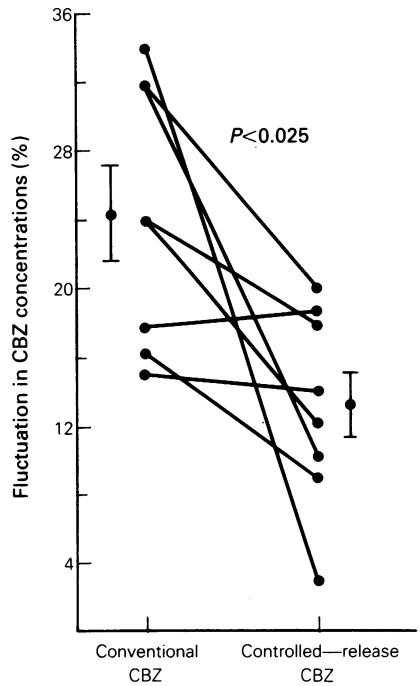

Figure 7 Diurnal fluctuation $\left(\frac{C_{max}-C_{min}}{mean}\right) \times 100\%$ of carbamazepine (CBZ) in eight subjects following conventional and controlled-release formulations.

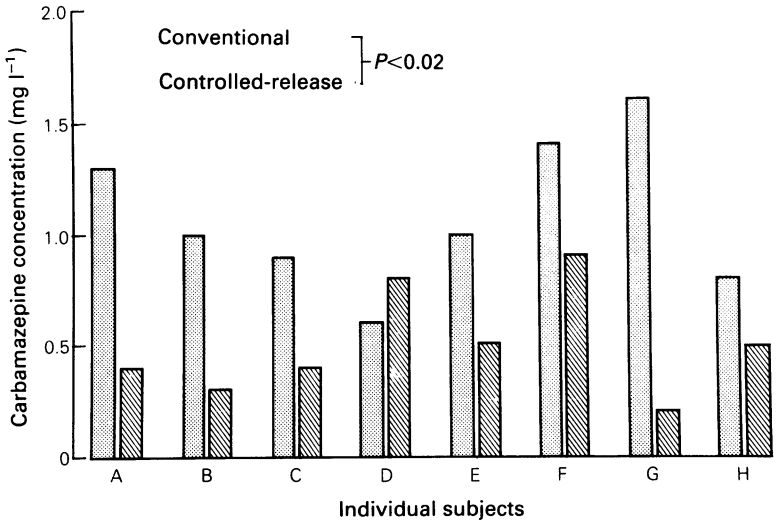

Figure 8 Maximum 2 h increment in plasma carbamazepine concentration in eight subjects following the 29th dose of conventional (▨) and controlled-release (▧) formulations.

Induction

The mean half-life of CBZ fell from 37 h (± 9.5) to 23 h (± 2.8) after 2 weeks of therapy with CBZ-C ($P<0.01$). After 2 weeks of treatment with CBZ-CR the half-life of CBZ (25 h ± 5.8) was similar to that with CBZ-C. The elimination half-life was incalculable in some subjects following single dose CBZ-CR as the concentration had not reached a terminal phase at 56 h. Antipyrine clearance was significantly induced by both preparations after 1 week's treatment, and was further increased at 2 weeks (Figure 9).

Psychomotor testing

No significant differences were found between the two preparations for any of the tests performed. Various comparisons were made, but for the sake of brevity, mean values for each study day are presented in Table 1.

Discussion

These results confirm a controlled-release profile for the CBZ-CR preparation, with a slow rise in CBZ concentration and a plateau from 6–56 h following a single dose. Diurnal fluctuation with conventional CBZ in patients has been variously estimated at 36% (Hoppener *et al.*, 1980), 41% (Riva *et al.*, 1984) and 59% (Macphee *et al.*, 1987). Our measure (24%) may be lower than these figures because of the strict adherence to a twice daily schedule by healthy volunteers. The controlled-release preparation showed an improvement on even this figure (12%) which should have a beneficial effect on the side-effects associated with large swings in blood drug concentration (Hoppener *et al.*, 1980; Riva *et al.*, 1984; Tomson, 1984). We have observed, both during this and other studies (Macphee *et al.*, 1986b) and in clinical practice, that many patients complain of maximum drowsiness and diplopia 30–120 min after ingestion of CBZ i.e. before peak drug concentrations are achieved. This suggests that a rapid increase in concentration may be important in initiating the mild neurotoxic side-effects associated with the drug. If this is the case, the smaller increments shown with CBZ-CR may be as relevant as the reduction in peak drug concentration or in overall fluctuation.

The contribution of CBZ-E to the psychotropic side-effects of CBZ is uncertain. The epoxide has similar efficacy to the parent compound in animal models of epilepsy (Faigle *et al.*, 1977) and is more potent than CBZ in the treatment of trigeminal neuralgia (Tomson & Bertilsson, 1984). While Post and his co-workers (1983) suggested that neither CBZ nor CBZ-E concentrations correlate with psychotropic side-effects, we have recently found a positive association for a number of measures of psychomotor impairment with the concentrations of

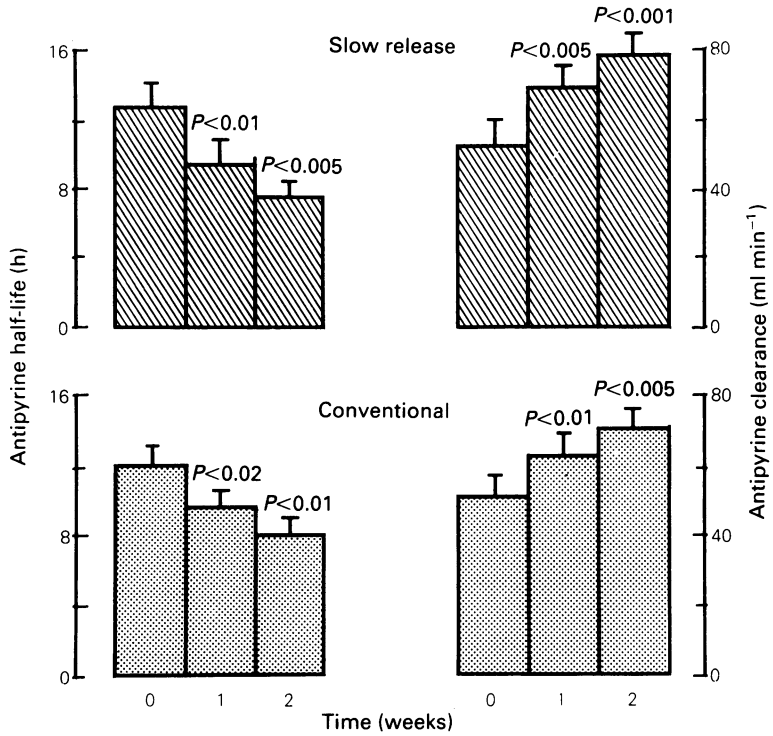

Figure 9 Effect of conventional and controlled-release ('slow release') carbamazepine on antipyrine half-life and clearance following 1 and 2 weeks of chronic therapy.

Table 1 Mean performance of psychomotor function tests (s.d.) in eight subjects receiving conventional and controlled-release carbamazepine for 2 weeks

		Conventional carbamazepine				*Controlled-release carbamazepine*			
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
C.f.f.t.i.	(Hz)	26.9 (2.8)	26.2 (3.1)	26.9 (2.1)	27.6 (1.9)	27.5 (2.3)	27.1 (2.0)	27.0 (1.7)	27.3 (2.1)
C.f.f.t.d.	(Hz)	28.4 (4.8)	27.5 (4.4)	28.6 (4.2)	28.9 (4.2)	28.8 (3.4)	28.4 (4.2)	28.3 (4.4)	28.5 (4.1)
CRT 1	(s)	0.342 (0.02)	0.338 (0.03)	0.338 (0.03)	0.331 (0.03)	0.342 (0.03)	0.342 (0.03)	0.334 (0.02)	0.334 (0.03)
CRT 2	(s)	0.484 (0.06)	0.481 (0.07)	0.486 (0.07)	0.475 (0.07)	0.490 (0.05)	0.480 (0.06)	0.480 (0.06)	0.471 (0.07)
Digit span	(n)	8.93 (2.2)	8.96 (1.6)	9.22 (1.4)	9.81 (2.3)	8.70 (1.8)	9.20 (1.9)	9.29 (1.7)	8.84 (3.2)
Card sorting	(s)	45.0 (5.0)	44.9 (4.1)	47.3 (6.3)	45.6 (7.3)	47.2 (6.9)	45.5 (6.2)	48.6 (6.7)	48.2 (6.6)
Finger tapping	(taps min^{-1})	389 (31.2)	391 (31.6)	378 (62.2)	387 (30.5)	389 (20.5)	396 (28.2)	373 (59.3)	392 (25.6)
Alertness score	(mm)	75.0 (12.6)	75.6 (15.8)	72.0 (18.2)	78.8 (15.9)	82.6 (12.6)	80.7 (9.5)	76.4 (11.8)	83.5 (10.6)

Columns 1 and 5 are calculated from the pre-dosing measurements (n = 16).
Columns 2 and 6 are from measurements following dosing on first day of chronic therapy (n = 24).
Columns 3 and 7 include all measurements on days 8 of chronic therapy (n = 32).
Columns 4 and 8 are obtained from all measurements on days 15 of chronic therapy (n = 32).
C.f.f.t. = critical flicker fusion threshold (i = increasing frequency; d = decreasing frequency).
CRT = choice reaction time (1 = recognition time; 2 = complete manoeuvre).

both substances, the relationship with the epoxide being the more impressive (Gillham *et al.*, 1988).

The decreased half-life of CBZ following 2 weeks of therapy with CBZ-C confirms previous reports that CBZ induces its own metabolism (Eichelbaum *et al.*, 1975; Rapeport *et al.*, 1983), sometimes necessitating an increase in dose to avoid breakthrough seizures (Macphee & Brodie, 1985). Since it is not known, however, whether the extent of induction is a function of peak, trough or steady-state drug concentrations, it is of interest to note that the mean half-life of CBZ following CBZ-CR (24.4 h) was similar to that found with CBZ-C (23.2 h). The effect of CBZ-CR on antipyrine clearance was more impressive than that of CBZ-C against baseline values, but there were no significant differences when the two preparations were compared directly.

The AUC over a dosage interval at steady state was 7% lower with CBZ-CR. Although this was not a statistically significant decrease we cannot exclude the possibility that the bioavailability of CBZ-CR may be slightly less than that of CBZ-C in epileptic patients receiving high doses of the drug (Kramer *et al.*, 1987). This difference is likely to be small, however, and would not explain the reduced fluctuation which was calculated as a percentage of the serum values. Increased induction with CBZ-CR might be postulated as a reason for decreased AUC, particularly since the AUCs after dose 15 were similar. No significant differences in CBZ half-life or antipyrine induction were found to support this suggestion.

The diurnal pattern of unbound CBZ concentrations was similar to that of CBZ and this would be expected since the extent of protein-binding was similar with both preparations. CBZ-E concentrations seemed 'tighter' and at a lower level with the CBZ-CR preparations than CBZ-C. However, these differences did not reach conventional levels of significance with the small numbers of subjects in this study. The smaller standard error bars with CBZ-CR reflect the significantly reduced variation in CBZ-E concentration between individuals on this preparation, rather than reduced diurnal fluctuation.

A battery of simple psychomotor function tests failed to reveal differences between the two preparations. This is not surprising as the variability of these tests would work against disclosing differences in small numbers of healthy volunteers taking a relatively low CBZ dose. Subjective complaints suggested that symptoms were not experienced at times of peak drug concentration, and so the timing of the psychomotor testing may have been less than optimal. These results argue against a large detrimental effect of CBZ at the dosage and blood drug concentrations obtained. Nevertheless, appropriate comparisons in epileptic patients may reveal a more stable pattern of cognitive function with a controlled release CBZ formulation (Aldennkamp *et al.*, 1987).

In this study we have shown that Tegretol CR Divitabs is indeed a controlled-release preparation of CBZ, with 'smoother' concentration-time curves resulting in less diurnal fluctuation at steady state. A study to relate this attractive pharmacokinetic picture to improvement in seizure control and psychomotor function in epileptic patients is under way.

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