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Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy

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Abstract—The in-vitro dissolution profiles of two carbamazepine formulations (Tegretol and a generic carbamazepine) have been assessed and the bioavailability of carbamazepine compared in 12 epileptic children at steady-state. Dissolution from the generic formulation (100 and 200 mg tablets) tended to be greater than for the proprietary tablets. However, the bioavailability and pharmacokinetics of carbamazepine when assessed at steady-state were similar for the two formulations. It appears, therefore, that the breakthrough seizures and higher incidence of neurological side-effects observed when children were given generic carbamazepine in place of the proprietary formulation cannot be accounted for by differences in bioavailability or pharmacokinetics.

Recently we started prescribing a new carbamazepine formulation (Ethical Generics, UK) in place of Tegretol (Ciba-Geigy) and found that two epileptic patients, who had been asymptomatic for more than two years relapsed in 3 and 7 days, respectively, following administration of the generic. Their seizures, however, were controlled when the generic was replaced by the proprietary formulation. Although this might have been coincidence, similar occurrences have been noted in patients changed to generic carbamazepine (Sachdeo & Belendiuk 1987; Shaheen et al 1989). Moreover, we have recently found that there is a higher incidence of neurological adverse effects in patients receiving generic carbamazepine (Hartley et al 1990). Those observations suggest that the bioavailability of generic carbamazepine might be erratic. This has prompted us to compare the in-vitro dissolution profiles of the two formulations, and their bioavailability at steady-state in epileptic children.

Materials and methods

Protocol. Ethical approval was given by the local Ethics Committee and parental consent was obtained. Twelve children (9 males and 3 females) aged between 6·5 and 15 years (mean age ± s.d.: 10·6 ± 2·8 years), who had at least 3 tonic-clonic or complex partial seizures, were studied. The sole drug treatment during the course of the study was carbamazepine given as 100 or 200 mg tablets twice daily. Patients received the same dose (200 to 500 mg/12 h) during both phases of the study and the mean dose relative to body weight was about 20 mg kg^{-1} day^{-1}. Allocation of the two formulations was randomized according to a list known only to the hospital pharmacy. The duration of each phase of the study was 6 weeks and this allowed for any auto-inductive effects to stabilize and for possible establishment of a new steady-state (Bertilsson et al 1986). At the end of 6 weeks treatment patients were admitted to hospital for blood sample collection. A blood sample was taken before the doses were given (0800 h; 0 h) and at 2, 3, 4, 8, 10 and 12 h afterwards using a peripheral venous cannula (Quickcath). A second course of tablets was given and patients were readmitted 6 weeks later for further blood samples to be collected.

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Dissolution studies. The absence of a dissolution test for carbamazepine tablets from the monographs of the British Pharmacopoeia (BP) and United States Pharmacopeia (USP) necessitated establishing dissolution criteria. However, Dam et al (1981) used 1 L of 0·1 M HCl as the dissolution media, so this was adopted. The amount of carbamazepine which dissolved in 1 L of 0·1 M HCl at 37°C during 120 min was determined using a 6 place Copley Dissolution Station coupled via a Watson Marlow 10-head peristaltic pump to a Beckman DU65 ultraviolet/visible spectrophotometer fitted with a 10 mm flow-through cell. Dissolution was achieved using the USP paddle mixing technique (paddle speed, 100 rev min^{-1}) and the solution was pumped through a sintered plastic filter at 11·0 mL min^{-1} (pump speed 50 rev min^{-1}) to remove particulate excipients before measurement of ultraviolet absorption at 314 nm (with automatic background subtraction using a wavelength of 350 nm). Twelve tests were carried out on each of the 100 and 200 mg tablets for each carbamazepine preparation, with simultaneous blank and standard determinations.

Assay of carbamazepine and its metabolites. Plasma concentrations of carbamazepine and two metabolites, carbamazepine epoxide (CBZ-EP) and carbamazepine diol (CBZ-DIOL), were measured by HPLC (Hartley et al 1987). Briefly, drug and metabolites were extracted from plasma (0·1 mL) using 1 mL capacity Bond Elut C_{18} columns. Components were eluted with acetone, the eluant evaporated to dryness and the residue reconstituted in mobile phase. Chromatography was carried out at room temperature (20°C) using a mobile phase of acetonitrile–methanol–water (19:37:44 v/v) in conjunction with a Nova-Pak C_{18} column (Waters Associates). Flow rate was 1·8 mL min^{-1} and the detection wavelength was 214 nm.

Analysis of results. The area under the concentration-time curve within a dose interval at steady-state (AUC) was calculated using the trapezoid rule. Standard equations (Rowland & Tozer 1980) were used to calculate the average concentration at steady-state (C_{av}) and the ratio of plasma clearance (CL) to availability (F). Relative bioavailability was obtained from the ratio of the AUC values for the two preparations. Peak concentration (C_{max}) and the time at which this occurred (t_{max}) are given as observed values. Results are shown as mean ± s.d. and statistical analyses were done using either the Mann–Whitney test (dissolution data) or Student's *t*-test for paired samples (pharmacokinetic data).

Results and discussion

Disintegration of the generic and proprietary tablets occurred almost immediately and of the total carbamazepine available, between 83 to 95% dissolved in 1 L of 0·1 M HCl at 37°C during the 120 min dissolution study (Fig. 1). The extent of dissolution found here for the 200 mg tablets of the proprietary (about 87%) was higher than the range of values (65–75%) reported by Dam et al (1981). Fig. 1 shows that solubility increased with the carbamazepine content of the generic such that 88·1 ± 4·3% ($n = 12$) dissolved from the 100 mg tablets and 95·4 ± 7·7% ($n = 12$; $P < 0.05$) dissolved when the 200 mg preparation was

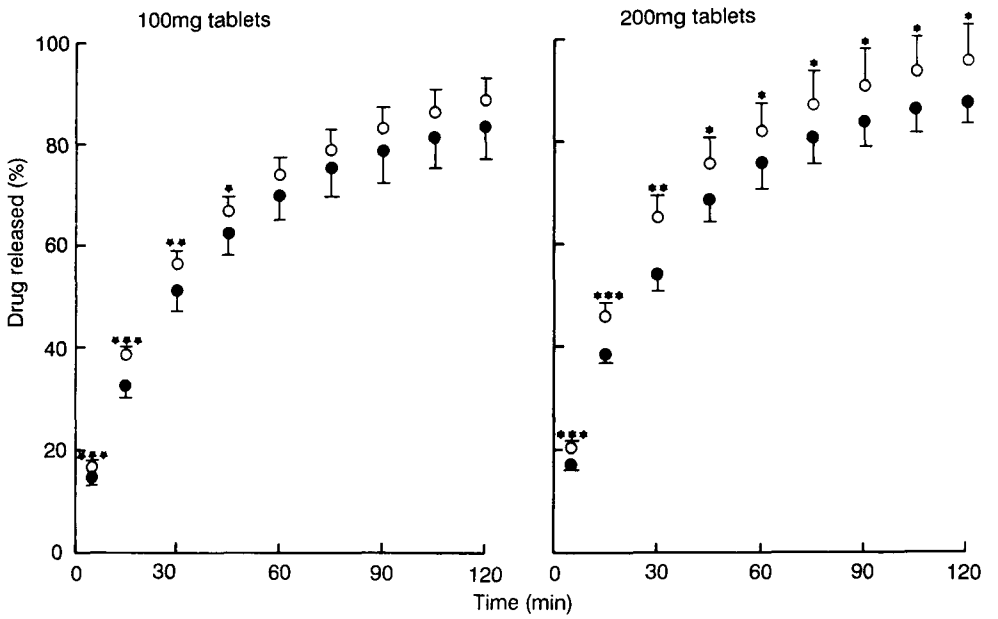

FIG. 1. Dissolution profiles of 100 and 200 mg tablets of generic (○) and proprietary (●) carbamazepine. The dissolution medium was 1 L of 0·1 M HCl at 37°C. Data are given as mean ± s.d. (n = 12). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

tested. Although the percent carbamazepine released from the 200 mg tablets of the proprietary appeared greater than with 100 mg tablets (87·1 ± 4·4% vs 82·8 ± 6·2%; n = 12, respectively) this difference was not statistically significant ($P > 0.05$).

Fig. 1 shows that over the first 45 min of the dissolution test, release of carbamazepine from the 100 mg generic tablets was greater ($P < 0.05$) than from the proprietary. But after 45 min, the percentage drug dissolved was not significantly different. With the 200 mg tablets there was a small, but significantly greater release of carbamazepine from the generic compared with the proprietary preparation over the duration of the dissolution test. Overall these results suggest that the rate of dissolution is greatest for the generic and since carbamazepine exhibits dissolution rate-limited absorption (Levy et al 1975), it might be anticipated that the generic carbamazepine would give better bioavailability than the proprietary carbamazepine.

Fig. 2 shows that there were no significant differences ($P > 0.05$) between plasma concentrations achieved during a single dose interval (12 h) at steady-state with the two preparations. A similar picture was obtained for levels of the metabolites CBZ-EP and CBZ-DIOL. It is interesting that there was little fluctuation of either CBZ-EP or CBZ-DIOL levels during the dosage interval for both preparations (Fig. 2). The peak to trough ratio for carbamazepine was about 1·5 whereas for CBZ-EP and CBZ-DIOL it was 1·3 and 1·0, respectively. In adults, the inter-dose variation in CBZ-EP levels is also less than the variation for carbamazepine (Ghose et al 1983; Loonen et al 1989). One explanation for this could be that at steady-state, the first order rate constants for the elimination of CBZ-EP and CBZ-DIOL are less than the elimination rate constant for the parent drug. Under this circumstance, peak to trough ratios for the metabolites are likely to be less than the corresponding ratio for parent drug (Houston 1986). The pharmacokinetic parameters obtained for both preparations are listed in Table 1. There were no significant differences in AUC, C_{av} or CL/F between the two preparations. In addition, relative bioavailability was about 1·0, suggesting that both formulations had the same extent of absorption. No differences in C_{max} or t_{max} were found: 10·2 ± 1·8 μg mL^{-1} and 3·6 ± 0·5 h, respectively for the proprietary, and 9·91 ± 2·31 μg mL^{-1} and 3·1 ± 0·7 h, respect-

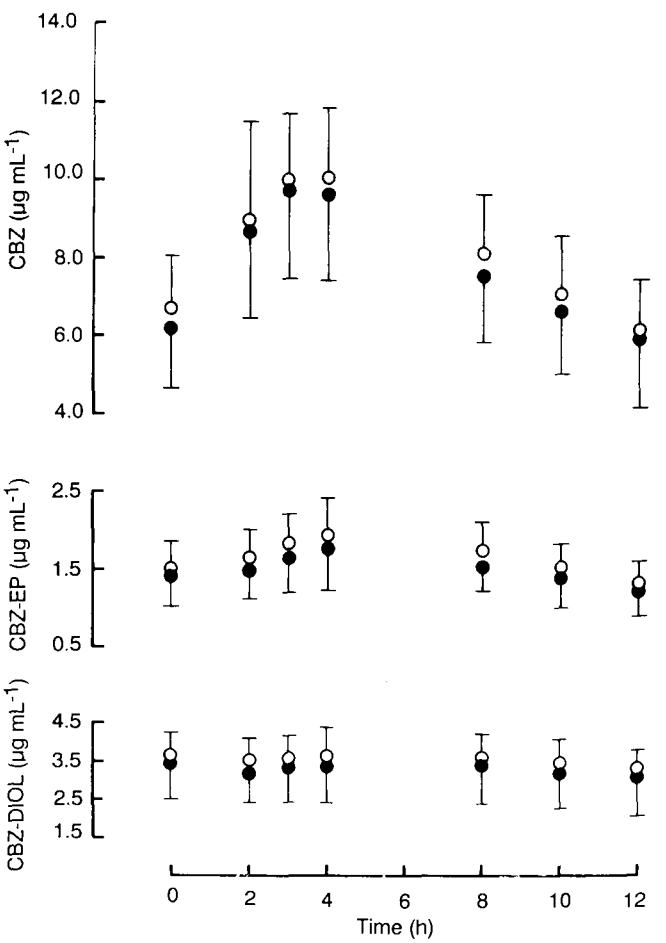

FIG. 2. Plasma concentrations of carbamazepine (CBZ), its epoxide (CBZ-EP) and diol (CBZ-DIOL) metabolites during a dose interval (12 h) at steady-state. Patients received either generic (●) or proprietary (○) carbamazepine. Data are shown as mean ± s.d. (n = 12).

Table 1. Summary of pharmacokinetic parameters for patients receiving proprietary and generic brands of carbamazepine.

Patient	Dose (mg)	Tegretol			Generic		
Patient		AUC (μg h mL^{-1})	CL/F (L h^{-1})	C_{av} (μg mL^{-1})	AUC (μg h mL^{-1})	CL/F (L h^{-1})	C_{av} (μg mL^{-1})
1	200	100	2·00	8·33	96·6	2·07	8·05
2	300	114	2·63	9·91	140	2·14	11·7
3	200	65·7	3·04	5·48	60·3	3·32	5·03
4	400	130	3·08	10·8	125	3·20	10·4
5	400	103	3·88	8·58	121	3·31	10·1
6	500	102	4·90	8·27	102	4·90	8·5
7	300	114	2·63	9·50	109	2·75	9·08
8	250	91·5	2·73	7·63	93·4	2·68	7·78
9	300	75·5	3·97	6·29	82·2	3·65	6·85
10	400	94·0	4·26	7·83	97·9	4·09	8·16
11	200	95·6	2·09	7·65	51·6	3·88	4·30
12	300	101	2·97	8·08	89·4	3·36	7·45
	Mean	98·9	3·18	8·20	97·4	3·28	8·12
	s.d.	17·0	0·89	1·46	25·4	0·81	2·12

ively for the generic. As the observed values of C_{max} and t_{max} are crude measures of the rate of absorption, this would indicate that the difference in the in-vitro rate of drug dissolution between the preparations had no detectable effect on the rate of absorption when assessed at steady-state.

In previous work we found a higher incidence of neurological side-effects, such as diplopia, headache, mood changes, slowing and tiredness, during treatment with the generic product (Hartley et al 1990). The present study demonstrates that this observation is unlikely to be due to differences in pharmacokinetics or bioavailability of the two carbamazepine formulations. CBZ-EP, the major metabolite of carbamazepine (Eichelbaum et al 1985), has anticonvulsant activity (Faigle et al 1977) and contributes to the incidence of neurotoxicity (Dam et al 1981; Patsalos et al 1985; Gillham et al 1988). No differences, however, were found in the plasma levels of CBZ-EP, or CBZ-DIOL, after treatment with the two preparations. Thus the higher incidence of neurotoxic effects in patients given the generic cannot be explained by changes in steady-state levels of the epoxide or diol metabolites.

Most studies of carbamazepine bioavailability have been done with single doses in healthy volunteers (Dam et al 1981; Shaheen et al 1989); on repeated administration carbamazepine induces its own metabolism (Bertilsson et al 1986), so data obtained from single dose studies might not be relevant in the context of prolonged therapy. By contrast, this study was conducted at steady-state in epileptic patients and as a consequence, the observation that the generic (Ethical Generics, UK) and proprietary (Tegretol, Ciba-Geigy) preparations have the same extent and rate of absorption and equivalent pharmacokinetics, is of direct clinical relevance to the treatment of children with epilepsy.

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