Bioequivalence of Carbamazepine Chewable and Conventional Tablets: Single-Dose and Steady-State Studies

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Abstract □ Single-dose and steady-state studies were carried out on separate occasions to examine the bioequivalence of the newly formulated carbamazepine chewable tablet. In the single-dose study, the plasma levels resulting from 2 × 200-mg conventional tablets (CT), 4 × 100-mg chewable tablets swallowed whole (SW), and 4 × 100-mg chewable tablets chewed before swallowing (CHEW) were compared. A randomized 3 × 3 Latin-square design balanced for residual effects, with a 3-week washout period, was used (n = 6). Plasma samples were analyzed by a specific GC method for carbamazepine. The following parameters were used for evaluation: AUC, C_{max}, t_{max}, and $t_{1/2}$. None of the parameters were significantly different except C_{max} and $t_{1/2}$ values for CHEW and CT. The C_{max} was 25% higher and $t_{1/2}$ was 11% shorter for CHEW than CT. The impact of differences in the peak plasma levels at steady state were examined by pharmacokinetic projection (400 mg b.i.d.) based on the single-dose data and with simulated induction equal to a 50% reduction in $t_{1/2}$. The projected steady-state CT and CHEW plasma concentrations were similar, with a difference of only 4%. The results demonstrate the bioequivalence of the dosage forms with respect to the extent of absorption, and similar steady-state concentrations of carbamazepine in plasma can be expected. To test the conclusion from the projected study, a separate bioequivalence study to compare CHEW relative to CT was performed at steady state in normal volunteers (200 mg b.i.d.). A randomized 2 × 2 crossover design was used, with each formulation being administered for 24 d followed by a 5-d sample collection period (n = 9). The plasma samples were analyzed by a specific HPLC assay for carbamazepine (CBZ) and the epoxide metabolite (CBZE). Predose levels (days 22–24) were not significantly different for either formulation. In addition, no period effect was observed on the $t_{1/2}$ of CBZ or on the metabolite fraction, indicating that induction was in a stable state and that steady state for CBZ plasma levels was reached. Again, the results demonstrate that both formulations delivered equal amounts of CBZ to the systemic circulation. The average C_{max} of CBZ for CHEW was 7% higher (6.4 versus 6.0 μg/mL) and the median t_{max} was slightly shorter (2.0 versus 3.0 h) than that for CT, but the differences were not significant. The results are in close agreement with those estimated in the projected study.

Carbamazepine (Tegretol; Geigy Pharmaceuticals, CIBA-GEIGY Corp.), an anticonvulsant agent used in the treatment of epilepsy[1] and trigeminal neuralgia,[2] is often used in children as the only antiepileptic medication. Recently, a chewable tablet has been developed for those patients who have difficulties in swallowing the conventional tablet. The present study was carried out to examine the bioequivalence of this newly formulated tablet that can be chewed prior to swallowing. Bioequivalence is defined as the determination of the relative bioavailability of the chewable tablet when compared to the conventional formulation as a standard, following single-dose administration and at steady state.

Experimental Section

Single-Dose Study—*Study Design and Subjects*—The study followed a single-dose, randomized 3 × 3 Latin-square design balanced for residual effect. Six healthy adult volunteers were fully informed of the procedures and the drug before signing consent forms; appropriate institutional approval was also obtained. Each volunteer received three 400-mg doses of carbamazepine as 2 × 200-mg conventional tablets (CT, lot H1662), 4 × 100-mg chewable tablets swallowed whole (SW, lot H1661), and 4 × 100-mg chewable tablets chewed for a period of 30 s before swallowing (CHEW, lot H1661). The sequence of drug administration for each subject was determined by random assignment. All subjects fulfilled protocol requirements at the time of selection. These requirements included normal physical examination and laboratory values. The subjects had no history of anemia, bone marrow depression, bleeding disorders, cardiovascular disease, asthma, hepatic or renal disease, drug dependence, alcoholism, and/or drug hypersensitivity. No drug treatment was allowed for 7 d prior to and during the study. The mean (± SD) age for the subjects was 35.7 ± 8.3 years, their mean weight was 164.3 ± 14.2 lbs. (74.8 ± 6.6 kg), and their mean height was 70.3 ± 1.2 in. (178.5 ± 4.2 cm). Blood samples were collected before medication and at 1, 2, 4, 6, 8, 12, 24, 32, 48, 72, 96, and 168 h postdose. Heparinized plasma was harvested and frozen immediately, and the samples were stored frozen until analysis.

Analytical Procedure—Plasma carbamazepine (CBZ) levels determined by a previously described GC method[3] provide a sensitive and specific determination for CBZ without interference. Experiments in which CBZ was added to control plasma prior to analysis showed an average recovery of 101.3 ± 4.7% in the range of 0.2–6.0 μg/mL. The limit of sensitivity was 0.05 μg/mL based on the reproducibility of the assay.

Pharmacokinetic Calculations—The peak plasma level (C_{max}) is the highest observed concentration, and t_{max} is the corresponding time of this concentration. The terminal half-life ($t_{1/2}$) was determined by least-squares regression analysis of the log-linear phase of the plasma level versus time data. The area under plasma level versus time curves from time zero to infinity ($AUC_{0-\infty}$) was calculated according to the linear trapezoidal rule up to the last measurable level, $C_{p,last}$, plus the residual area, calculated by $C_{p,last} \cdot t_{1/2}/0.693$.

Statistical Analysis—AUC, C_{max}, and $t_{1/2}$ were examined by analysis of variance of a 3 × 3 Latin-square design balanced for residual effects[4] and with multiple comparisons using the procedure of Scheffe[5] which utilizes formulation means corrected for residual effects. In addition, two types of 95% confidence limits were calculated for the corrected means of the AUC, Westlake's confidence interval[6] and Shirley's confidence interval.[7] The t_{max} was analyzed by nonparametric analysis including Friedman's two-way analysis disregarding sequence and residual effect, and with multiple comparisons based on Friedman's ranked-sum test.[8] A p value of <0.05 and confidence intervals of >20% of the difference in formulation means were considered to be significant.

Pharmacokinetic Projection Based on the Single-Dose Data—Individual pharmacokinetic parameters, *FD/Vd*, k_a, and k_{el}, were obtained by fitting the single-dose plasma level versus time data to eq. 1 by the nonlinear regression analysis program NONLIN:[9]

$$C(t) = \frac{FD}{Vd} \frac{k_a}{k_a - k_{el}} (e^{-k_{el}t} - e^{-k_a t}) \quad (1)$$

where $C(t)$ is the plasma concentration at any time t, FD is the fraction of the dose absorbed, Vd is the apparent volume of distribution, and k_a and k_{el} are the apparent absorption and elimination rate

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constants, respectively. Individual projected steady-state concentrations, $C_{ss}(t)$, were calculated by:

$$C_{ss}(t) = \frac{FD}{Vd} \frac{k_a}{(k_a - k_{el,ss})} \left(\frac{e^{-k_{el,ss}t}}{1 - e^{-k_{el,ss}T}} - \frac{e^{-k_a t}}{1 - e^{-k_a T}} \right) \quad (2)$$

where $C_{ss}(t)$ is the steady-state plasma concentration at any time during the dosing interval (T = 12 h for an assumed regimen of 400 mg every 12 h), and $k_{el,ss}$ is the steady-state elimination rate constant. The $k_{el,ss}$ value is equal to $2k_{el}$ when autoinduction is assumed. The apparent volume of distribution, Vd, is assumed to be constant during the study.

Steady-State Study—*Study Design and Subjects*—The study was performed after the single-dose study and was designed to test the conclusion from the projected study by a comparison of steady-state plasma levels when 200 mg of carbamazepine was administered twice daily as CT or as CHEW. The study followed a randomized 2 × 2 crossover design with each formulation administered for 24 d followed by a 5-d sample collection period. Ten healthy adult volunteers were fully informed about the procedures and the drug before signing consent forms; appropriate institutional approval was also obtained. Each volunteer received doses of carbamazepine in a 200 mg b.i.d. (every 12 h) regimen as 1 × 200-mg conventional tablets swallowed whole (CT) or as 2 × 100-mg chewable tablets chewed for 30 s before swallowing (CHEW). All subjects fulfilled protocol requirements (same as the single-dose study) at the time of selection. The mean (± SD) age for the study subjects was 40.2 ± 6.8 years, their mean weight was 75.9 ± 11.6 kg, and their mean height was 181.9 ± 6.3 cm. The subjects reported to the study unit after overnight fasting on each study day. Blood samples were collected according to the following schedule: (day 0) 0 h (predose) blood samples and first formulation started; (day 22) 0 h; (day 23) 0 h; (day 24) 0 h (final dose of first formulation administered) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 48, 56, 72, 97, and 120 h postdose.

Immediately after the 120-h specimen was obtained, the alternate formulation was started and the entire routine was repeated. Heparinized blood samples were centrifuged, and the plasma was separated and frozen immediately; samples remained frozen until analysis. A total of nine subjects completed both phases of the study.

Analytical Procedures—Plasma levels of carbamazepine (CBZ) and its metabolite, carbamazepine-10,11-epoxide (CBZE), were analyzed by a specific HPLC method. A description of the analytical methodology and a detailed validation of the assay, including data on precision (within-run and run-to-run reproducibility), accuracy, sensitivity, linearity, and specificity, has been reported.[10]

Calibration curves for CBZ and CBZE were constructed daily during the course of the present study. All calibration curves (n = 10) afforded a correlation coefficient (r) of 0.999 or better. Day-to-day precision in the analysis of CBZ is characterized by CVs of 0.51–7.0% over the range of the standard curve. The corresponding values for CBZE were 2.4–10.4%. The CVs of the slopes of the CBZ and CBZE daily calibration curves were 5.5 and 9.8%, respectively, demonstrating good reproducibility of response over the 41-d period during which the samples were analyzed.

At the beginning of the study, plasma samples spiked with known amounts of CBZ and CBZE were prepared (n = 40). These were analyzed periodically throughout the study for quality control of the analytical method, as well as indication of the stability of the samples under storage conditions. The quality-control samples were analyzed in groups of four along with the study samples. Mean values of recovery ranged from 94.1 to 103.1% for CBZ and from 90.0 to 99.0% for CBZE over the entire range of concentrations analyzed. These results show good control of the analytical method and stability of plasma samples over the period of the study.

Approximately 10% of the plasma samples (n = 38) were analyzed in duplicate, and the mean differences between the duplicate samples were 3.2 ± 3.1% (maximum 13%) for CBZ and 4.8 ± 4.0% (maximum 20%) for CBZE. These results provide additional evidence for the good reproducibility of the assay.

Pharmacokinetic Calculations—Pharmacokinetic parameters calculated for the CBZ (and CBZE, where applicable) plasma concentration–time data and their method of determination are given below:

1. C_{max} was determined as the maximum concentration during the 12-h dosing interval examined on day 24.
2. t_{max} was determined as the time at which C_{max} occurred. When adjacent concentrations are equal to C_{max}, the median time is taken as t_{max}.
3. C_{min} was taken as the concentration observed 12 h after dosing on day 24.
4. The 0 h (predose) concentration is the concentration determined just prior to administering the morning dose on days 22–24.
5. AUC_{0-12} was determined for both CBZ and CBZE as the area under the plasma concentration–time curve over the 12-h interval on day 24, calculated by the trapezoidal rule.
6. The $t_{1/2}$ was determined for both CBZ and CBZE by linear regression analysis of the log concentration versus time using data from 24 h to the last measurable concentration. The time frame corresponds to the washout period following the administration of the last dose of each formulation.
7. $\bar{C}_{ss}$ is defined as the time-averaged plasma concentration at steady state and was determined by the AUC_{0-12} divided by the dosing interval (12 h).
8. Mr is defined as the metabolite fraction and was determined as the ratio of the area under the curve for metabolite CBZE relative to that for the parent drug CBZ over the 12-h dosing interval on day 24.
9. F_r is defined as the relative bioavailability and was determined as the ratio of AUC_{0-12} for the chewable tablet relative to that for the conventional tablet.

Statistical Analysis—Zero-hour plasma concentrations on days 22–24 were examined by analysis of variance with appropriate contrasts to assess steady state. Half-life ($t_{1/2}$) was analyzed by the Wilcoxon signed-rank test[11] on paired replicates disregarding sequences. AUC_{0-12}, C_{max}, and $t_{1/2}$ values were analyzed by analysis of variance[12] with a correction for unequal numbers of subjects in each treatment sequence. In addition, Westlake's confidence limits[6] were calculated for the difference in formulation means (adjusted for imbalance). A p value of <0.05 and Westlake's confidence limits of >20% were considered to be significant in this study.

Results and Discussion

Single-Dose Study—No signs and symptoms attributable to the drug were seen after CT. Three subjects complained of symptoms after SW and two subjects complained of symptoms after CHEW. The symptoms were mild (tiredness, dizziness, sedation, and inability to concentrate), the durations were short, and the symptoms disappeared in ~0.5 h in most cases. One subject, after SW, complained of mild substernal pain just before breakfast (2 h postdose); the symptoms disappeared after the subject had eaten. No clinical examinations or laboratory studies performed during or after this study showed any changes.

Mean concentration versus time values of CBZ in plasma of six subjects after a 400-mg dose are displayed in Fig. 1. Samples collected at time zero (predose) were found to contain no detectable CBZ. Mean pharmacokinetic parameters determined from analysis of the single-dose data are presented in Table I. The AUC values for the three regimens were comparable, indicating bioequivalence with respect to AUC. After corrections for the residual effects, the only

Table I—Mean Pharmacokinetic Parameters for Carbamazepine after a Single 400-mg Dose under Different Conditions

Parameter	2 × 200-mg Conventional Tablets (CT)	4 × 100-mg Chewable Tablets (SW)	4 × 100-mg Chewable Tablets (CHEW)
$AUC_{0-\infty}$, μg · h/mL	215.0 (215.8)[a] ±25.5[b]	225.0 (223.8) ±28.8	231.3 (231.7) ±36.7
C_{max}, μg/mL	3.24 (3.36) ±0.49	3.72 (3.65) ±0.61	4.23 (4.19) ±0.63
t_{max}, h	8[c] (4–32)	6[c] (4–24)	6[c] (4–12)
$t_{1/2}$, h	34.3 (35.1) ±4.2	31.8 (31.8) ±3.0	32.0 (31.2) ±4.7

[a] Mean corrected for residuals is in parentheses. [b] Standard deviation. [c] Median value; range is in parentheses.

parameters which were significantly different from each other were the C_{max} and $t_{1/2}$ values for CHEW and CT (C_{max} 4.19 versus 3.36 μg/mL and $t_{1/2}$ 31.2 versus 35.1 h). The data for CHEW showed significantly higher C_{max} (+25% at p = 0.05) and significant shorter $t_{1/2}$ (−11% at p = 0.05) than those obtained from CT. The results demonstrate the equivalence of the two dosage forms with respect to the extent of absorption.

Projection Study—To examine the impact of the difference in peak plasma levels at steady state for CT and CHEW, a projection was carried out based on the information obtained from the single-dose study, with and without simulated induction. Since no significant differences were found between CT and SW, the projection was not performed for SW. After examination of each data set, a one-compartment open model appeared to be appropriate. Curve fitting was done with equal weighting, with weighting of reciprocal concentration, and with deletion of data points which appeared to be outliers. The two latter measures did not result in improvement of the parameter estimates. The parameter resulting from weighting of one and inclusion of all data points were chosen for further calculation (Table II). The values for k_{el} are in good agreement with those reported by Gerardin et al.[13]

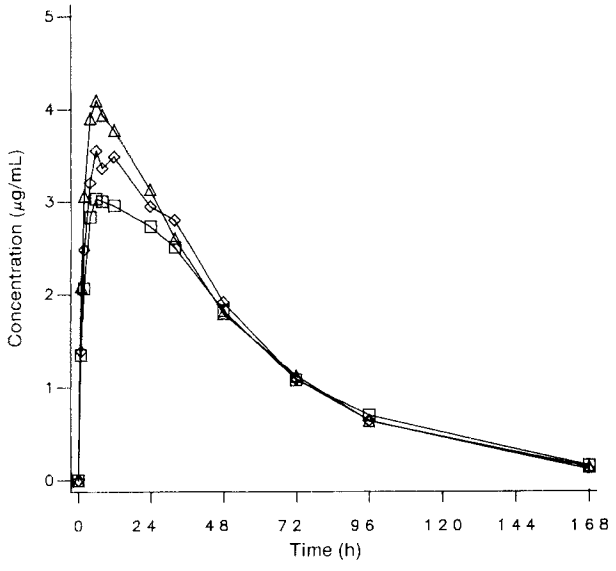

Figure 1—*Mean concentration of carbamazepine in plasma of six subjects after a single 400-mg dose. Key:* (□) *2 × 200-mg conventional tablets (CT);* (◇) *4 × 100-mg chewable tablets (SW);* (△) *4 × 100-mg chewable tablets (CHEW).*

It has been well established that the half-life of carbamazepine decreases after repeated dosing, and this is generally attributed to an increased rate of elimination due to enzyme induction.[14] Although the extent of induction varies considerably in different published studies, induction was assumed to decrease the elimination half-life by 50% for the present simulation. This is not unreasonable based on published information.[13,15–17] A 12-h dosing interval was selected because CBZ is often administered in a b.i.d. dosing regimen. Projected steady-state concentrations without simulated induction were also calculated to serve as baseline values. The mean projected steady-state concentrations of CBZ in plasma indicate that similar steady-state concentrations can be expected from both formulations. Steady-state maxima calculated without simulated induction averaged 20.3 μg/mL for CT and 20.8 μg/mL for CHEW; this is a difference of only 2%. With simulated induction equivalent to a 50% decrease in half-life, the mean steady-state maxima were 10.5 μg/mL for CT and 11.0 μg/mL for CHEW, a difference of 4% (Table III).

Steady-State Study—*Clinical Observations*—When carbamazepine was first administered, eight subjects reported mild side effects (tiredness, disorientation, floating feeling, and/or malaise). No subjects fell asleep, and all were able to perform their duties at work. Within a few days, these symptoms decreased greatly in severity. When drug administration was stopped, all subjects felt better. When drug was readministered, symptoms were much milder regardless of the sequence of formulation.

All but 1 of the 10 subjects completed the study. The subject who was dropped from the study completed the first phase of the study (chewable tablet). However, when the drug was restarted with the conventional tablet, itching and a blotchy red rash were noted following the third dose, and the drug was stopped after the fourth dose. The rash and itching diminished rapidly and was not noticeable 5 d after the drug was discontinued. The liver enzyme levels were elevated slightly at the time of the rash and returned to normal quickly. Plasma concentration–time data for this subject was not used to calculate parameter means and standard deviations, nor were they used in the statistical analysis of the data.

Plasma Concentration–Time Data—The predose concentration–time data for days 22–24 for both formulations are

Table II—Pharmacokinetic Parameters for NONLIN Curve Fitting of Carbamazepine in Plasma after a Single 400-mg Dose as Conventional Tablets (CT) and Chewable Tablets (CHEW)

Subject	k_a, h^{-1}	k_{el}, h^{-1}	*FD/Vd*, μg/mL	Lag Time, h	r
		Conventional Tablets (CT)			
1	0.934 (0.057)[a]	0.018 (0.008)[a]	4.14 (0.07)[a]	—	0.999
2	0.519 (0.110)	0.014 (0.002)	3.44 (0.16)	1.6 (0.2)	0.995
3	0.617 (0.121)	0.013 (0.002)	3.79 (0.21)	—	0.991
4	0.409 (0.098)	0.022 (0.002)	3.82 (0.33)	—	0.993
5	0.446 (0.152)	0.011 (0.002)	2.59 (0.27)	—	0.997
6	0.356 (0.059)	0.016 (0.002)	3.71 (0.22)	—	0.993
		Chewable Tablets (CHEW)			
1	0.630 (0.176)	0.020 (0.002)	5.15 (0.29)	0.7 (0.2)	0.991
2	1.004 (0.200)	0.018 (0.002)	4.18 (0.20)	—	0.996
3	0.710 (0.070)	0.017 (0.002)	5.21 (0.16)	—	0.998
4	0.326 (0.017)	0.028 (0.001)	5.60 (0.10)	0.5 (0.0)	1.000
5	0.846 (0.123)	0.017 (0.002)	3.65 (0.13)	—	0.996
6	1.115 (0.050)	0.020 (0.000)	4.10 (0.04)	—	1.000

[a] Standard deviation of parameters estimated are in parentheses.

summarized in Table IV. Linear plots of the mean concentration–time data for CBZ and CBZE for all subjects who completed the study are depicted in Fig. 2. The mean plasma level data over the 12-h dosing interval for both formulations are also presented in Fig. 2. The pharmacokinetic parameters determined from analysis of the data for CBZ and CBZE are summarized in Table V.

Evidence to Support the Attainment of Steady State—Because CBZ has been shown to induce its own metabolism during the early phase of chronic therapy in humans,[14] the subjects in this study were maintained on a fixed regimen of 200 mg of CBZ every 12 h for a period of 24 d. To verify that steady state was achieved, three criteria were used:

1. Analysis of variance and trend analysis of the predose CBZ plasma levels on days 22, 23, and 24.
2. Comparison of $t_{1/2}$ for the first and second treatments (phase I and phase II), independent of formulation, using a paired t test, as well as examination of the "period effect" in the analysis of variance.
3. Comparison of the metabolite fraction (Mr) for the first and second treatment, independent of formulation, using a paired t test.

Analysis of the predose levels on days 22–24 showed no significant difference and no significant linear or quadratic trend over the 3-d period for either formulation, suggesting that steady state was in fact achieved. In addition, no period effect in the half-life of CBZ was observed in the analysis of variance, and the $t_{1/2}$ was not significantly different between the first and second phases of treatments. This finding supports the view that induction is in a stable state during

Table III—Mean Projected Steady-State C_{max} and C_{min} Concentrations of Carbamazepine in Plasma

Dosage Form	Without Simulated Induction		With Simulated 50% Decrease in Half-Life	
	C_{min}, μg/mL	C_{max}, μg/mL	C_{min}, μg/mL	C_{max}, μg/mL
Conventional tablets (CT)	18.37 ±3.10[a]	20.30 ±3.20	8.61 ±1.54	10.53 ±1.64
Chewable tablets (CHEW)	17.99 ±3.19	20.80 ±3.48	8.20 ±1.51	10.99 ±1.81
	(2% Difference in C_{max})		(4% Difference in C_{max})	

[a] Standard deviation.

Table IV—Predose Plasma Levels of Carbamazepine (CBZ) and Carbamazepine-10,11-epoxide (CBZE) after 1 × 200-mg Conventional Tablet (CT) or 2 × 100-mg Chewable Tablets (CHEW) Every 12 h

	Plasma Level, μg/mL			
	Day 22	Day 23	Day 24	Overall
CBZ				
CHEW	5.0 ± 0.7	4.8 ± 0.6	4.8 ± 0.6	4.9 ± 0.6
CT	4.8 ± 1.1	5.0 ± 0.6	5.1 ± 0.7	5.0 ± 0.8
Phase I[a]	5.1 ± 1.0	5.0 ± 0.7	5.1 ± 0.8	5.1 ± 0.8
Phase II[a]	4.8 ± 0.9	4.9 ± 0.5	4.8 ± 0.5	4.8 ± 0.6
CBZE				
CHEW	0.62 ± 0.10	0.59 ± 0.09	0.60 ± 0.07	0.60 ± 0.08
CT	0.53 ± 0.12	0.57 ± 0.08	0.61 ± 0.10	0.57 ± 0.10
Phase I[a]	0.58 ± 0.12	0.60 ± 0.08	0.63 ± 0.09	0.60 ± 0.10
Phase II[a]	0.57 ± 0.12	0.56 ± 0.08	0.58 ± 0.09	0.57 ± 0.09

[a] First and second phases of treatment, independent of formulation.

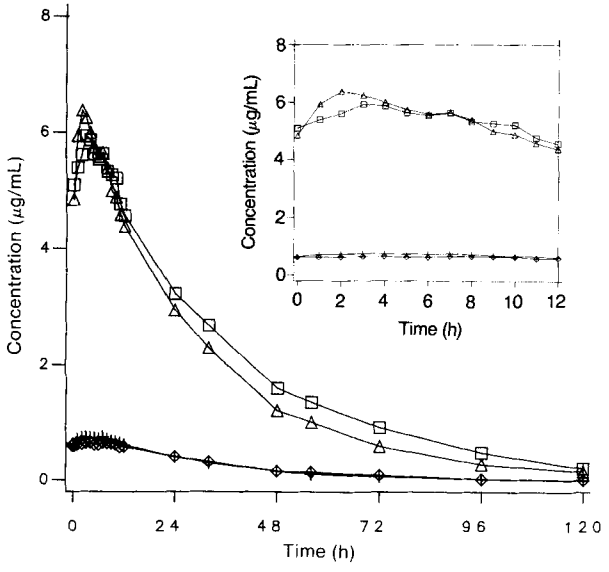

Figure 2—*Mean steady-state plasma concentrations of carbamazepine (CBZ) and carbamazepine-10,11-epoxide (CBZE) for all completed subjects following the study dose. The inset is the mean plasma concentrations following the study dose over the 12-h dosing interval. Key: (□) CBZ [conventional tablet (CT)]; (△) CBZ [chewable tablet (CHEW)]; (◇) CBZE (CT); (+) CBZE (CHEW).*

Table V—Pharmacokinetic Parameters as Determined from Steady-State Plasma Levels of Carbamazepine (CBZ) and Carbamazepine-10,11-epoxide (CBZE) after 1 × 200-mg Conventional Tablet (CT) or 2 × 100-mg Chewable Tablets (CHEW) Every 12 h

	CBZ		CBZE	
	CHEW	CT	CHEW	CT
Mean C_{max} (μg/mL)	6.4 ± 0.9	6.0 ± 0.7	0.78 ± 0.14	0.69 ± 0.09
Median t_{max} (h)	2.0 (1.0–7.0)[a]	3.0 (2.0–9.0)	4.0 (1.0–10.0)	4.0 (3.0–10.0)
Mean AUC (0–12) (μg · h/mL)	65.4 ± 9.0	65.0 ± 7.6	8.1 ± 1.4	7.5 ± 1.0
Mean $t_{1/2}$ (h)	24.3 ± 4.3 (26.8 ± 2.3)[b]	27.3 ± 2.8 (24.8 ± 4.9)[b]	20.6 ± 4.0 (20.8 ± 5.4)[b]	22.7 ± 10.1 (22.5 ± 9.4)[b]
Mean C_{min} (μg/mL)	4.4 ± 0.6	4.6 ± 0.6	0.60 ± 0.12	0.58 ± 0.07
Mean $\bar{C}_{ss}$ (μg/mL)	5.4 ± 0.7	5.4 ± 0.7	—	—
Mean C_{max}/C_{min}	1.47 ± 0.08	1.32 ± 0.07	1.31 ± 0.07	1.19 ± 0.07
Mean F_r[c] (%)	100.2 ± 13.7 (80.0–123.4)[a]	—	108.7 ± 12.5 (92.9–131.0)	—
Mean Mr[d]	—	—	0.12 ± 0.007 (0.12 ± 0.010)[b]	0.12 ± 0.01 (0.12 ± 0.009)[b]

[a] Range is in parentheses. [b] First and second phases of treatment, independent of formulation. [c] Relative bioavailability. [d] Metabolite fraction.

the final days of the first and second treatments. If any additional induction-related increases in clearance occur during this period, a significantly shorter half-life of CBZ would be expected during the second treatment, irrespective of treatment order. This was not found to be the case.

If induction of drug-metabolizing enzymes is associated with the formation of CBZE from parent CBZ, the metabolite-to-drug AUC ratio would be altered during the period of increasing induction. Thus, a comparison of metabolite fraction, Mr, during the two treatment phases should show a significant increase during the second phase over that measured during the first phase. This was not observed in the study, thus providing additional evidence for the lack of changing induction during the two treatment periods (Table V). It is concluded that induction, if it occurred during this study, was essentially complete by the time the first phase of the study was completed.

Assessment of Bioequivalence—Relative bioavailability of the chewable tablet compared to the conventional tablet was determined as F_r, the ratio of CBZ AUCs over the 12-h dosing interval at steady state. AUC_{0-12} values averaged 65.4 ± 9.0 μg/mL · h for CHEW and 65.0 ± 7.6 μg/mL · h for CT. They were not significantly different by analysis of variance. Westlake's confidence limits were ±11.1% of the mean of the CT. The relative bioavailability, as measured by the ratio of the AUC_{0-12} values for CHEW with respect to CT, averaged 100.2 ± 13.7%. These results demonstrate that both formulations deliver equivalent amounts of drug to the systemic circulation.

Peak plasma concentrations of CBZ for CHEW are slightly higher (6.4 ± 0.9 μg/mL) than for CT (6.0 ± 0.7 μg/mL), but the difference between them (7%) was not significant. This difference in the means of the C_{max} values is considerably less than that observed (25%) in a single-dose study and is in close agreement with that estimated in a projection study (4%). Time-to-peak values, as evaluated by the Wilcoxon signed-rank test on paired replicates disregarding sequence, were not different. This comparison, coupled with the finding that the C_{max}/C_{min} ratio was slightly higher for CHEW than that for CT (1.47 ± 0.08 versus 1.32 ± 0.07), suggests the possibility of a small but insignificant difference in absorption rate between the two formulations, with the chewable tablet demonstrating slightly more rapid absorption of CBZ.

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