The Bioinequivalence of Carbamazepine Tablets with a History of Clinical Failures

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The bioavailability of three lots of a generic 200-mg carbamazepine tablet, which had been withdrawn from the market, was compared to the bioavailability of one lot of the innovator product in 24 healthy volunteers. Fifty-three lots of the generic product had been recalled by the manufacturer because of concerns over reports of clinical failures for several of the lots. The three generic lots tested in this study exhibited a wide range of bioavailability, as well as large differences in the *in vitro* dissolution rates. The mean maximum carbamazepine plasma concentrations for two of the generic lots were only 61–74% that of the innovator product, while the third lot was 142% of the innovator. The mean areas under the plasma concentration–time curve for the three generic lots ranged from 60 to 113% that of the innovator product. The results clearly indicate a significant difference in the rate and extent of absorption of the generic products compared to the innovator, as well as among the generic lots. A good relationship was found between the *in vivo* parameters and the *in vitro* dissolution results for the four dosage forms.

KEY WORDS: carbamazepine; human; bioavailability; pharmacokinetics; dissolution.

INTRODUCTION

Carbamazepine is a widely prescribed anticonvulsant drug, which has been available as a generic product since 1986. Several reports have appeared concerning incidents of seizures in patients who were apparently stabilized on the innovator product and subsequently received a generic product (1,2). However, others (3) have compared one generic product to the innovator product at steady state in patients and found no difference in bioavailability or efficacy. During the fall of 1988 a recall of 200-mg carbamazepine tablets was initiated by one generic firm, involving 53 different lots, representing approximately 70 million tablets. The recall was based on several reports of clinical failures of the product, as well as observed changes in the dissolution characteristics of the marketed products.

The objective of this study was to evaluate the bioavailability of three lots of the recalled generic product to determine the relationship between the *in vitro* dissolution results and the bioavailability of the products.

METHODS

Subjects. Twenty-four healthy, nonsmoking males were enrolled in the study, ranging in age from 21 to 35 years and weighing 61 to 93 kg. All subjects had normal clinical chemistry laboratory values, including reticulocyte count and serum iron.

Carbamazepine Products. Three lots of the 200-mg generic carbamazepine tablets, Pharmaceutical Basics, Inc., Lot no. K583-01 (Product 2), F844-07 (Product 3), and F915-03 (Product 4) were provided by U.S. Food and Drug Administration (FDA). The innovator 200-mg tablets, Geigy Pharmaceuticals, Inc., Lot. No. 1T108912 (Product 1), was purchased locally.

Protocol. The clinical study protocol was approved by the Institutional Review Board and the Risk Involving Human Subject Committee of the FDA. The subjects did not ingest any drugs for 21 days and avoided alcohol for 48 hr prior to each dose of carbamazepine. The 24 subjects were randomly divided into four groups, and each group received a single 200-mg dose of each of the four products in a different sequence. A 21-day interval elapsed between each dose. After an overnight fast, each subject received one of the products along with 180 ml of room-temperature water. No food was allowed until a standard meal was served 4 hr after dosing. Ten-milliliter blood samples were obtained through a heparin lock or direct venipuncture just before dosing and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 25, 49, 73, 97, 121, and 169 hr after dosing. The first 1 ml of blood was discarded prior to each 10 ml collection if a heparin lock was employed. The blood was centrifuged, and the plasma fraction was stored at $-20°C$ until assayed.

Plasma Assay. The determination of plasma carbamazepine (Sigma Chemical, Inc.) concentrations was based on modifications of the HPLC method of Riad and Sawchuck (4). A 0.5-ml plasma sample was adjusted to pH 11 and extracted with 10 ml of 1.5% isoamyl alcohol in chloroform. Cyheptamide (Alltech/Applied Science, Inc.) was employed as the internal standard. Samples of 10,11-epoxide carbamazepine (Alltech/Applied Science, Inc.) were also chromatographed to test for potential interference from this metabolite.

Pharmacokinetic Data Analysis. The typical pharmacokinetic parameters of area under the plasma concentration–time curve to 196 hr (AUC 0–196), AUC to infinite time (AUC 0–∞), time of maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), and terminal rate constant (K) were computed using standard techniques (5). The fraction absorbed calculations employed the Wagner–Nelson Method (6), applied to the individual carbamazepine plasma concentration–time data. The statistical analysis employed a SAS program with a general linear model for treatment, period, sequence, and subject (sequence) effects.

Dissolution Testing. The *in vitro* dissolution testing employed the USP method (7), which utilizes the paddle method at 75 rpm, with 900 ml of water containing 1% so-

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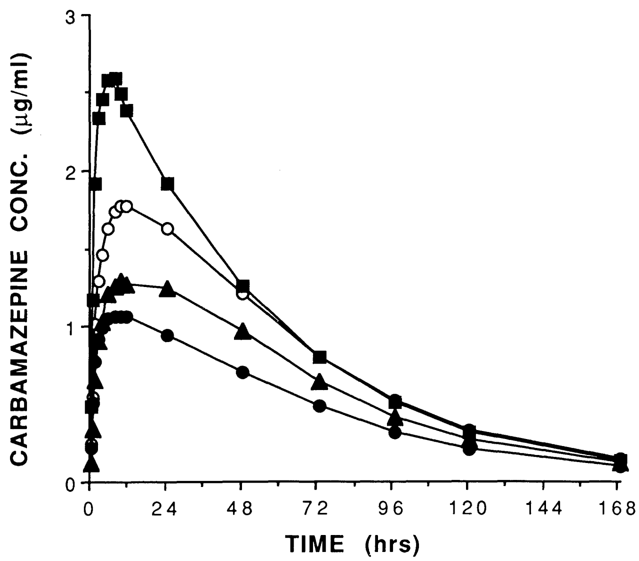

Fig. 1. Mean carbamazepine plasma concentrations. (○) Product 1; (●) Product 2; (■) Product 3; (▲) Product 4.

dium lauryl sulfate. Six tablets of each product were tested, and samples of the dissolution media were removed at 15, 30, 45, 60, and 90 min.

In Vivo–in Vitro *Relationships.* The relationship between the *in vitro* dissolution data and the *in vivo* pharmacokinetic data was examined by plotting the percentage of drug dissolved after 30, 60, and 90 min and the percentage absorbed data (F_A) calculated 30, 60, and 90 min after dosing. A value for the percentage absorbed at 90 min was estimated from a linear regression of a plot of Ln $(1 - F_A)$ versus time at 30, 60, and 120 min since plasma samples were not obtained 90 min after dosing. Plots were also constructed for the mean maximum plasma concentration and mean AUC (0–∞) versus mean percentage dissolved at 15, 30, 45, and 60 min.

RESULTS

Twenty-two subjects successfully completed all four phases of the study. Two subjects were dropped from the study after the first phase because of transient low reticulocyte counts. They were replaced with two alternates, who completed all four study phases 3 weeks later than the other subjects. One subject was dropped from the study after completing the third phase because of a transient low reticulocyte count. A second subject withdrew after the third phase for personal reasons unrelated to the study. Subject complaints were relatively minor and did not result in any withdrawals from the study. The reported statistical analysis is based on the data for all 24 subjects. A separate analysis using only the 22 subjects completing all four phases gave essentially identical results.

Carbamazepine was chromatographically well separated (~3.5 min) from its major metabolite, carbamazepine 10,11-epoxide (~5.8 min), and the internal standard (~8.5 min). The assay was linear ($r > 0.99$) over a plasma concentration range of 0.05–4.0 μg/ml. A concentration of 0.05 μg/ml was the lowest quantifiable value. No plasma concentrations were less than 0.1 μg/ml until after the 121-hr sample. The analysis of triplicate fortified plasma quality-control samples containing 0.43, 1.6, and 3.1 μg/ml of carbamazepine, along with each set of unknown plasma samples, indicated good accuracy and precision. A total of 87 control samples was assayed for each of the three concentrations and the between-day and within-day CV% was <10 and <4%, respectively.

The mean carbamazepine plasma concentrations are illustrated in Fig. 1. The statistical analysis indicated significant differences ($P < 0.01$) among the four products at every sampling time. The mean pharmacokinetic parameters are summarized in Table I. Table II summarizes the statistical analysis of these data, employing the Newman Kuels a posteriori test to identify differences among specific products. Table II also provides a comparison between each product in terms of 90% confidence limits, using the two, one-sided test (8). Autoinduction of metabolism can occur for carbamazepine during chronic dosing (9). In the present study there was no evidence of enzyme induction. There were no significant differences ($P > 0.05$) in the apparent elimination rate constant (K) for the four study phases (range, 0.0179–0.0183 hr^{-1}). The 11% difference among the mean values for K for the four dosage forms was significant ($P < 0.05$). At least part of the difference could be attributed to a prolonged absorption phase for these products. Figure 2 illustrates the *in vitro* dissolution profiles for the four products. Figure 3 shows the relationship of the percentage absorbed versus the percentage dissolved for each product. Figure 4 illustrates the relationship between the *in vitro* test results and the *in vivo* values for AUC(0–∞) for the four products included in this study. Similar plots, which are not shown, using C_{max} as the *in vivo* parameter, also resulted in a good correlation: r^2

Table I. Mean Carbamazepine Pharmacokinetic Parameters

Parameter	Product 1 (N = 24)		Product 2 (N = 24)		Product 3 (N = 23)		Product 4 (N = 23)	
C_{max} (μg/ml)	1.89	(20)[a]	1.15	(62)	2.69	(18)	1.40	(39)
T_{max} (hr)	15.9	(51)	13.6	(74)	8.3	(72)	19.6	(78)
AUC(0–169) (μg · hr/ml)	134.8	(15)	80.9	(48)	154.2	(18)	104.5	(30)
AUC(0–∞) (μg · hr/ml)	143.5	(15)	86.5	(47)	162.2	(20)	111.7	(29)
K (hr^{-1})	0.0183	(15)	0.0173	(19)	0.0191	(16)	0.0177	(16)

[a] CV% in parentheses.

Table II. Statistical Analysis

Newman Keuls a posteriori analysis				
Parameter	Product ranking (lowest to highest)*			
C_{max}	2	4	1	3
T_{max}	3	2	1	4
AUC(0–∞)	2	4	1	3
K	3	1	4	2

90% confidence limits (two, one-sided test)		
Parameter	Product comparison	90% confidence interval
C_{max}	2 vs 1	48 to 73%
	3 vs 1	129 to 154%
	4 vs 1	61 to 86%
AUC(0–∞)	2 vs 1	51 to 69%
	3 vs 1	103 to 121%
	4 vs 1	69 to 114%

* Products underlined by the same line are not significantly different ($P > 0.05$).

= 0.98, 0.95, 0.89, and 0.83 for C_{max} versus percentage dissolved in 15, 30, 45, and 60 min, respectively.

DISCUSSION

In order for a generic product to be approved by the FDA and rated therapeutically equivalent, the 90% confidence limits for the mean AUC and C_{max} of the generic product must usually be within 80–120%, relative to the innovator product. The results obtained in this study demonstrate that the three lots of the generic product (Products 2, 3, and 4) are not bioequivalent to the innovator product (Product 1) and are not even bioequivalent to each other. The mean maximum carbamazepine plasma concentrations for the three generic lots ranged from 61 to 142% compared to the innovator product, and the mean areas under the plasma concentration–time curve ranged from 60 to 113%. Since the therapeutic range for carbamazepine plasma concentrations at steady state is narrow, 4–12 μg/ml (9), bioavailability differences of this magnitude are particularly significant for this drug.

The USP specification for carbamazepine tablets requires that not less than 75% of the drug be dissolved within 60 min. Both Product 2 and Product 4 fail this requirement. However, Product 3, which passes the USP specifications, is more rapidly dissolved than the innovator product, and exhibits a correspondingly larger value for C_{max} and AUC(0–∞). The apparently more rapid absorption of this product may have clinical significance in view of the report by Neuvonen (10), who observed a greater incidence of side effects (dizziness and ataxia) for rapidly absorbed carbamazepine tablets available in Finland. These results suggest that the USP specifications should be revised to also test for products that may be dissolving too rapidly.

Recently it has been proposed that a 1:1 (Level A) relationship between *in vitro* dissolution and *in vivo* absorption is the most desirable type of correlation for extended-release dosage forms (11). A Level C correlation, which involves a plot of *in vitro* dissolution data, such as the percentage dissolved at a certain time, and a single pharmacokinetic parameter such as AUC or C_{max} is considered to be less useful. The carbamazepine tablets employed in the present study were not intended to provide for an extended release, although two of the lots did exhibit slow dissolution. Figure 3 illustrates an attempt at a Level A, 1:1 *in vivo–in vitro* correlation and demonstrates a potential pitfall in the a priori reliance on *in vitro* data to predict *in vivo* bioavailability. Even though all four products demonstrate a linear relationship between the percentage dissolved and the percentage absorbed, no one relationship could be employed to predict the bioavailability of all four products. In contrast, the simpler relationships between the percentage dissolved, partic-

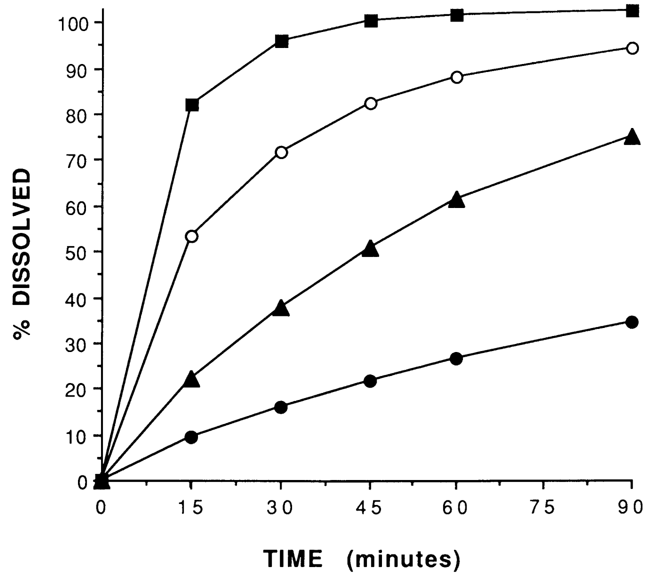

Fig. 2. Dissolution profiles for four 200-mg carbamazepine tablet products. (○) Product 1; (●) Product 2; (■) Product 3; (▲) Product 4.

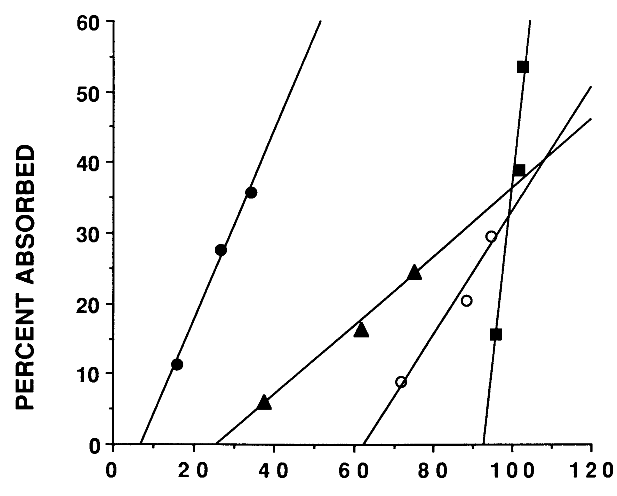

Fig. 3. Relationship between the mean percentage absorbed *in vivo* and the percentage dissolved *in vitro* at 30, 60, and 90 min for the four 200-mg carbamazepine tablet products. (○) Product 1; (●) Product 2; (■) Product 3; (▲) Product 4.

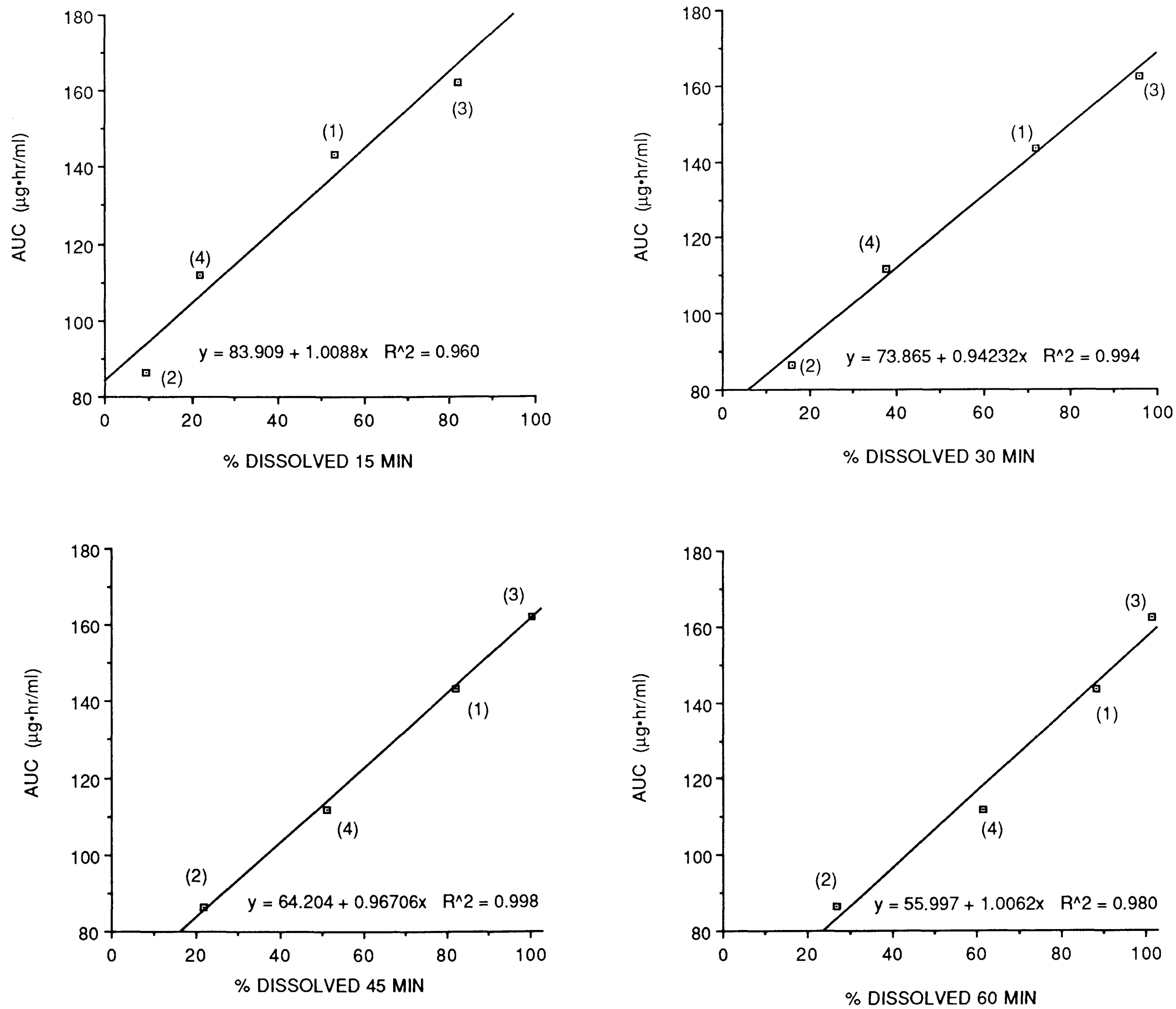

Fig. 4. Relationship between the mean AUC(0–∞) and the percent dissolved *in vitro* at 15, 30, 45, and 60 min. Product code numbers in parentheses.

ularly during the first 45 min, and the C_{max} and AUC values were quite useful in predicting the bioinequivalence of the four products. An inconsistency was also observed when attempts were made to relate the T_{max} and the percentage dissolved *in vitro*. Even though Product 2 exhibited the slowest dissolution, the mean T_{max} for this product was smaller by 2.3–6 hr compared to those for Products 1 and 4, respectively, as shown in Table I. Since the mean C_{max} and AUC were the lowest for Product 2, the intermediate T_{max} for Product 2 suggests that a portion of the dose was absorbed relatively rapidly compared to Products 1 and 4, but the extent of absorption, as well as the *in vitro* dissolution, was significantly lower for this product.

In the case of the specific tablets included in this investigation, other work (12) has indicated that an increase in the moisture content of the tablets during storage may, at least in part, be the reason for the significant differences in both the dissolution and the bioavailability of different lots of the generic product. In addition, the manufacturer has suggested that changes in the source of the carbamazepine raw material and differences in the particle size of the material employed for different lots may have also been a contributing factor (13).

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REFERENCES

1. G. Koch and J. Allen. Untoward effects of generic carbamazepine therapy. *Arch Neurol.* 44:578–579 (1987).
2. R. Sachdeo, S. Chokroverty, and G. Belendiuk. Risk of switching from brand-name to generic drugs in seizure disorder. *Epilepsia* 28:581 (1987).
3. A. Jumao-as, I. Bella, B. Craig, J. Lowe, and R. M. Dasheiff. Comparison of steady-state blood levels of two carbamazepine formulations. *Epilepsia* 30:67–70 (1989).
4. L. E. Riad and R. J. Sawchuk. Simultaneous determination of carbamazepine and its epoxide and trans-diol metabolites in

plasma by microbore liquid chromatography. *Clin Chem.* 33:1863–1866 (1988).
5. K. S. Patrick, A. B. Straughn, E. J. Jarvi, G. R. Breese, and M. C. Meyer. The absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. *Biopharm. Drug Disp.* 10:165–171 (1989).
6. J. G. Wagner. *Fundamentals of Clinical Pharmacokinetics, Drug Intelligence,* Hamilton, IL, 1975, pp. 174–177.
7. *United States Pharmacopeia.* United States Pharmacopeia Convention, Rockville, MD, 1989, p. 223.
8. D. J. Schuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokin. Biopharm.* 15:657–680 (1987).
9. R. H. Levy, A. J. Wilensky, and P. N. Friel. Other antiepileptic drugs. In W. E. Evans, J. J. Schentag, and W. J. Jusko (eds.), *Applied Pharmacokinetics,* Spokane, WA, 1986, pp. 540–569.
10. P. J. Neuvonen. Bioavailability and central side effects of different carbamazepine tablets. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 23:226–232 (1985).
11. *Pharmacopeial Forum.* The United States Pharmacopeial Convention, Washington, DC, 1991, Vol. 17, pp. 2222–2234.
12. J. T. Wang, G. K. Shiu, W. Worsley, C. T. Viswanathan, and J. P. Skelly. Effect of humidity and temperature on *in vitro* performance of carbamazepine tablets. *Pharm Res.* 7:S143 (1990).
13. R. Hartman. Personal communication, *Pharmaceutical Basics,* Denver, CO, July 6, 1990.