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Bioavailability of Carbamazepine from Four Different Products and the Occurrence of Side Effects[1]

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ABSTRACT: The relative bioavailability of four different carbamazepine products, showing large differences in *in vitro* dissolution profiles, was studied in healthy volunteers to correlate the occurrence of side effects with a measure of the rate of absorption *in vivo* for bioequivalence testing. Two of the three generic products investigated showed bioequivalence with respect to the extent of absorption with Tegretol®. *In vivo*, the differences found in absorption rate were reflected in the occurrence of side effects, especially dizziness. As a measure for the rate of absorption, the partial AUC did not seem to be a good characteristic to test bioequivalence, as the variability is very high and dependent on the AUC taken. The C_{max}/AUC_{part} seems more promising, especially the partial AUC directly after completion of the absorption process. The variability is low in the case of carbamazepine after a single dose. However, as long as no consensus on the use of other metrics and the objective (clinical or quality control aspects) of bioequivalence testing is reached, and no other pharmacokinetic characteristic is validated, C_{max} should be the characteristic of choice for the rate of absorption in single-dose studies with carbamazepine products.

Key words: carbamazepine; bioequivalence; rate of absorption; side effects; interchangeability

Introduction

Carbamazepine is used for its anti-epileptic activity, mainly in patients with partial epilepsy. It is also used in case of neuralgia and manic depression.

In the last few years several publications [1–5] were written in which the occurrence of side effects after changing from one carbamazepine product to another are described. In different countries experiments were started to find some explanations for this phenomenon [6–8]. These studies showed that the occurrence of side effects is not related to the extent of absorption. However, these studies also seem to indicate that between-product differences in the rate of absorption might be responsible for the occurrence of side effects, especially if patients switch from one product to another. When a study on this subject with products on the market in the Netherlands [9] was published a warning was issued in the Summary of Products Characteristics (SPC) of registered immediate-release carbamazepine products that changing between products could induce side effects.

In normal practice this phenomenon is not recognized in the application procedure for generic carbamazepine products. In earlier years, registration of carbamazepine products was mainly focused on the extent and less on the rate of absorption. Looking closer at the data submitted in the registration processes of carbamazepine products in the Netherlands a possible explanation for the occurrence of side effects and the loss of seizure control might be differences in the rate of absorption.

From most studies in the literature, conducted with healthy volunteers and a single dose, it is difficult to make a good estimate of the absorption rate as the study designs were not developed for this purpose. The absorption rate of carbamazepine given in the literature is very low resulting in t_{max} values of about 24–32 h. The variability in the t_{max} and C_{max} values is considered partially due to inter-product and inter-subject variation but also caused by inadequate study design for a good estimate of C_{max} and t_{max}. Using the published data no good relationship between a pharmacokinetic variable reflecting the absorption rate, and the occurrence of side effects could be established. The aim of this study was to examine the pharmacokinetics of four oral products registered in the Netherlands which contain carbamazepine. This single-dose study, undertaken in healthy volunteers, focused on the estimation of the rate of absorption and the extent of bioavailability and any possible relationship between these parameters and the occurrence of side

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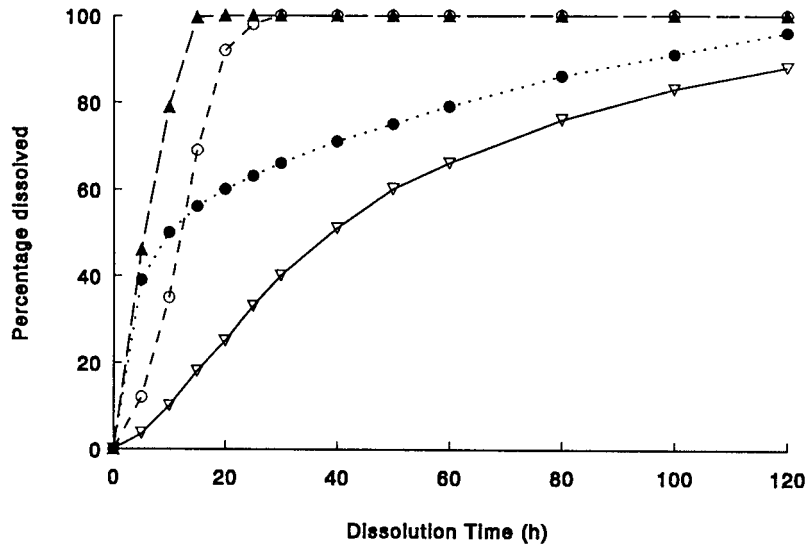

Figure 1. Dissolution profiles of four carbamazepine 200 mg products in 1% lauryl sulphate (Paddle method): ▽, product A; ○, product B; ▲, product C; ●, product D

effects. The three generic products were chosen as in a pilot study they showed large differences in *in vitro* dissolution times in comparison with the innovator product Tegretol®. The results of a similar study involving patients under steady-state conditions will be published separately. With the results of these studies it is hoped that better guidelines can be developed for the registration of generic carbamazepine products and the issuing (or not) of special warnings in the SPC text.

Materials and Methods

Subjects

Eighteen healthy, non-smoking volunteers, ranging in age from 20 to 38 years, weighing 49 to 88 kg, were enrolled in this study. All volunteers had given their written consent. The results of routine laboratory tests on blood and urine of the volunteers were within normal ranges. Sixteen volunteers completed the study. One volunteer was withdrawn after occurrence of a serious vasovagal collapse and one withdrew for personal reasons not related to the products.

Products

Three 200 mg carbamazepine products with large differences in dissolution rates in 1% lauryl sulphate (Figure 1), as well as the innovator product Tegretol®, were included in the study: Carbamazepine 200 mg Pharmachemie, Lot no. 92 A 21 NF (product A); Carbamazepine 200 mg Centrafarm, Lot no. 92 E 18A (product B); Pharbita, Lot no. 920401 (product C) and Tegretol Ciba Geigy 200 mg, Lot no. 92 F 22 (product D). All products are licensed in the Netherlands and were purchased from the pharmacy of the Utrecht University Hospital, the Netherlands.

Quality Assurance

The clinical part of the experiment was carried out under the OECD principles of GCP and the laboratory tests were carried out under GLP rules.

Study Design

The study protocol was approved by the Ethical Committee of the Utrecht University Hospital, the Netherlands. None of the volunteers were currently receiving medication. The volunteers were required to abstain from the use of alcohol from 24 h prior to the first study day until the end of the study. The administration of the drugs was accomplished in a four-way randomized cross-over design with washout periods between administrations of 2 weeks. The volunteers stayed in the hospital from 1 h before administration of the drug until 32 h postdose. Before administration the volunteers fasted overnight. The products, two tablets of 200 mg, were taken in the morning of the first study day of the sessions with 150 mL water. To exclude an attendant pregnancy, pregnancy tests were performed for female volunteers on the first day of each session before administration of the products.

Blood samples were taken in heparin test-tubes just before dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28 and 32 h postdose through an intravenous cannula. After 32 h the cannula was removed and at time points 48, 56, 72, 80 and 96 h postdose samples were taken by vena punction. Blood was directly centrifuged and the plasma stored at -70°C until analysis.

After administration of the products the volunteers were instructed to sit in an upright position

Table 1. Mean ($\pm$S.D., for t_{max}: median and range) pharmacokinetic characteristics of four different carbamazepine products after administration of 400 mg as a single dose to 16 volunteers calculated with a non-compartmental method and according to an open two-compartment model

Product		AUC_{0-96h} ($mg \cdot h\ L^{-1}$)	$AUC_{0-\infty}$ ($mg \cdot h\ L^{-1}$)	C_{max} ($mg\ L^{-1}$)	t_{max} (h)	$t_{1/2,abs}$ (h)	$t_{1/2,el}$ (h)	MRT_{abs} (h)	MRT (h)
A	Non-compartmental	198 ± 48	246 ± 61	3.2 ± 1.0	16 (4–48)		39 ± 7		62 ± 11
	model		243 ± 58	3.2 ± 1.0	16 ± 6.5	16 ± 10	30 ± 11	23 ± 14	
B	Non-compartmental	253 ± 73	294 ± 84	5.9 ± 1.6	4 (1.5–24)		34 ± 6		51 ± 10
	model		297 ± 91	5.6 ± 1.6	5.6 ± 5.9	3.8 ± 7	33 ± 5	6 ± 11	
C	Non-compartmental	253 ± 53	292 ± 69	6.1 ± 1.6	3 (1–24)		32 ± 5		48 ± 8
	model		299 ± 84	5.9 ± 1.6	3.6 ± 4.1	1.9 ± 5	34 ± 6	3 ± 7	
D	Non-compartmental	249 ± 44	295 ± 59	4.5 ± 0.8	8 (1.5–32)		34 ± 5		54 ± 6
	model		295 ± 58	4.3 ± 0.7	11 ± 5.2	13 ± 8	29 ± 10	29 ± 10	

for the first 4 h. Standardized meals were taken 4 and 10 h postdose.

Throughout the study the volunteers were asked to report side effects such as headache, dizziness, ataxia, diplopia, fatigue, drowsiness, nausea, and abdominal pain. The side effects were scored every hour and classified as (1) clearly present, (2) weakly present (3) unclear and (4) absent.

Analytical Method

Carbamazepine, carbamazepine-10,11-epoxide and 10,11-hydroxy-carbamazepine were determined in plasma with an HPLC method adopted from the Epilepsy Centre Kempenhaeghe, Heeze, the Netherlands (J.A.R.J. Hulsman, personal communication).

In short, 0.2 mL plasma samples were extracted with 8 mL dichloromethane after adding phenytoin as internal standard. After evaporation of the organic phase the residue was redissolved in 0.2 mL mobile phase and 50 μL was injected in the HPLC system with a Hypersil MOS 5μ column (200×4.6 mm). The mobile phase consisted of methanol–acetonitrile–Sorensen buffer (pH 7.0) (28:5:67). The method was validated for all three components. The limit of quantitation for all three compounds was 0.02 $\mu g\ mL^{-1}$ plasma.

The method was linear over the range of 0.05–6 $\mu g\ mL^{-1}$ plasma and the variability less than 10%.

Pharmacokinetic Analysis

The pharmacokinetic characteristics were calculated using standard non-compartmental methods by the program TopFit [10]. An open two-compartment model with first order absorption and elimination processes was fitted to the plasma concentration–time data also using this program.

The areas under the plasma concentration–time curves were calculated with the linear trapezoidal rule. The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were obtained directly from the plasma concentration–time data. The $AUC_{0-\infty}$ was calculated by dividing the last measured concentration (C_t) by the elimination rate constant (k_{el}) and adding the result to the AUC_{0-t}. The elimination rate constant was calculated by least-squares regression using the last six time points of each curve. The apparent elimination half-life was the quotient of the natural logarithm of 2 and the elimination rate constant.

The Mean Residence Time (MRT) was estimated by AUMC/AUC in which the AUMC is the area under the first moment curve.

Statistics

The pharmacokinetic data of interest were subjected to analysis of variance to detect differences between treatments, subjects and periods. The log-transformed ratios of the AUC and C_{max} were used testing for bioequivalence with the 90% confidence intervals of the two one-sided tests [11] and a non-parametric method [12].

In vitro

Dissolution of the tablets *in vitro* was studied using the United States Pharmacopeia (USP) method. The paddle apparatus was used operating at 75 rpm. The dissolution medium was 900 mL 1% sodium lauryl sulphate in water at 37.0 ± 0.5°C. Concentrations of carbamazepine were determined by UV absorbance measurement at 285 nm.

Results

For all four products the mean values of the relevant pharmacokinetic data of carbamazepine are listed in Table 1. In Figure 2 the individual plasma concentration–time curves for the four products are graphically presented and in Figure 3 the mean plasma concentrations of carbamazepine and the two main metabolites for all four products are shown. From Figure 2 it is clear that the variability in the plasma concentration–time curves after administration of the products is fairly small. Only

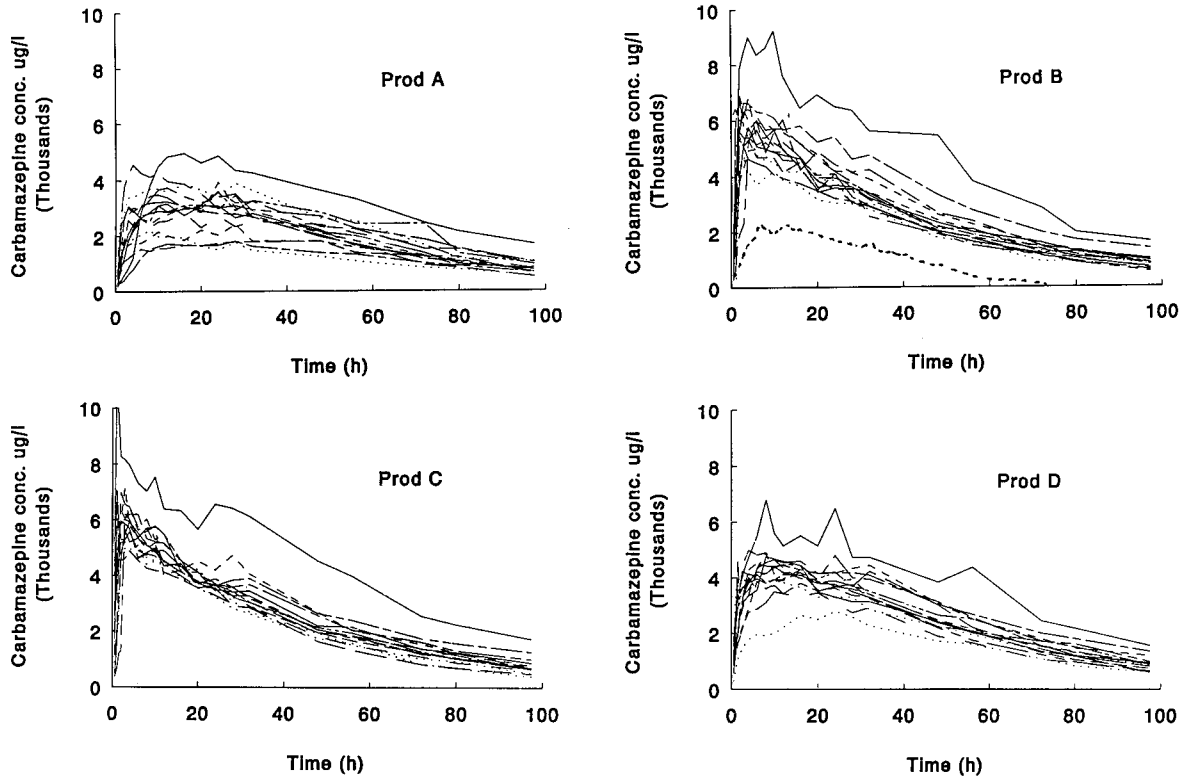

Figure 2. Individual plasma concentration–time curves of carbamazepine after administration of 400 mg of four different products in 16 healthy volunteers

one subject ($\#1$) had higher plasma levels in all four cases but could not be considered as an outlier. After administration of product B another volunteer showed very low plasma concentrations. All pharmacokinetic characteristics obtained with product A are statistically significantly different ($p < 0.05$) from the reference product D. Product B does not show any significant difference from product D. For product C all pharmacokinetic characteristics except the AUC values are significantly different ($p < 0.05$) from product D.

In Table 2 the pharmacokinetic characteristics of the 10,11-epoxide metabolite are given. The apparent half-lives found for the epoxide are in the same order as those found for carbamazepine suggesting that disappearance of the epoxide is dependent on its formation from carbamazepine.

As the aim of this investigation was to investigate possible correlations between the occurrence of side effects and pharmacokinetic characteristics, especially those reflecting the rate of absorption, partial AUC values and the C_{max}/AUC_{part} were calculated. The coefficients of variation of C_{max}/AUC_{part} were calculated to investigate the influence of the partial AUC on the quotient calculated. This is graphically shown in Figure 4.

To estimate the rate of absorption an open two-compartment model with first order rate constants of absorption and elimination was fitted to the data (see Table 1).

The occurrence of side effects in the volunteers after administration of the four products is listed in Table 3. Only the scores 'clearly' and 'weakly present' are given as no 'unclear' effects were reported by the volunteers.

In Table 4 the results of the statistical tests on bioequivalence are given. All these tests were carried out after log transformation of the data. From these tests it can be concluded that product A is not bioequivalent with the reference product D and products B and C are equivalent with respect to the extent of absorption. For C_{max} none of the products are bioequivalent with product D.

Discussion

The most important objective of bioequivalence testing is to guarantee patients that generic products are safe and clinically effective within certain boundaries. In the past a lot of discussion has taken place about the 'goalpost' for the acceptance of bioequivalence and what measure best reflects the rate of absorption [13–15]. In the case of carbamazepine products this rate of absorption may be especially important. Carbamazepine is very sensitive to moisture and the grade of hydration influences the dissolution *in vitro* as well as *in vivo* [16–19]. This altered rate of dissolution may cause serious side effects (e.g. dizziness, ataxia, sedation,

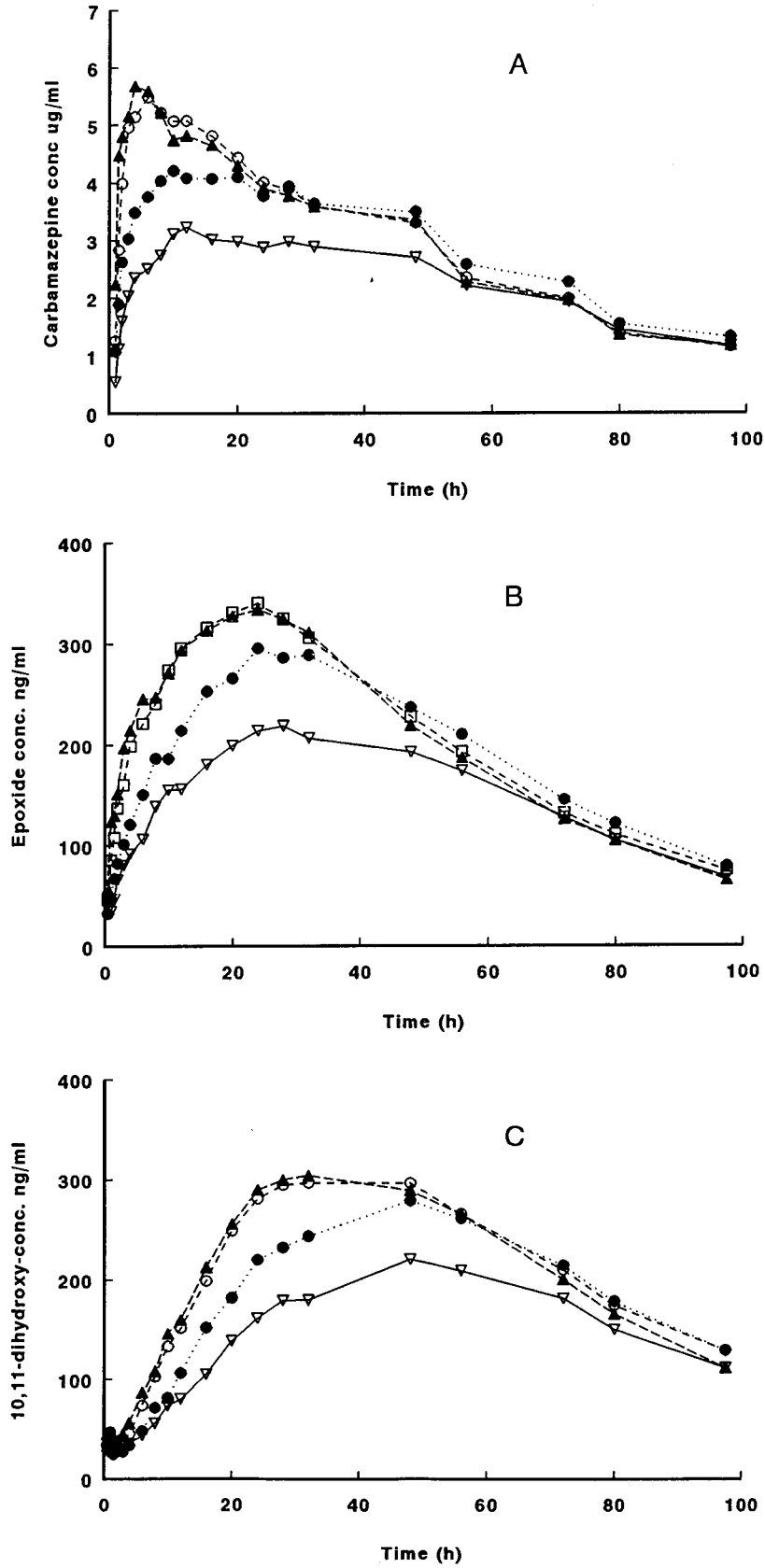

Figure 3. Mean plasma concentration–time curves of: A, carbamazepine; B, carbamazepine-10,11-epoxide; C, 10,11-hydroxy-carbamazepine after administration of 400 mg carbamazepine as four different products: ▽, product A; ○, product B; ▲, product C; ●, product D

Table 2. Mean ($\pm$S.D., for t_{max}: median and range) pharmacokinetic characteristics of carbamazepine-10,11-epoxide after administration of four different carbamazepine products as 400 mg as a single dose to 16 volunteers

Product	AUC_{0-96h} ($mg \cdot h\ L^{-1}$)	$AUC_{0-\infty}$ ($mg \cdot h\ L^{-1}$)	C_{max} ($mg\ L^{-1}$)	t_{max} (h)	$t_{1/2}$ (h)
A	14.7 ± 4.7	19.1 ± 5.5	259 ± 94	26 (8–56)	39 ± 11
B	20.0 ± 7.9	23.6 ± 6.6	354 ± 112	20 (10–48)	32 ± 4.9
C	19.8 ± 4.1	22.9 ± 4.2	352 ± 93	18 (12–28)	31 ± 11
D	18.7 ± 3.9	22.8 ± 4.6	317 ± 71	28 (16–32)	35 ± 6.3

double vision) and an increase in seizure frequency in patients changing from one product to another with different dissolution characteristics [1,20–24]. In normal bioequivalence testing for the registration of generic products the rate of absorption is measured as the C_{max} and t_{max} in healthy volunteers. As both pharmacokinetic characteristics are heavily dependent on the study design and C_{max} is also influenced by the extent of absorption, a new measure and corresponding criteria should be formulated for bioequivalence to ensure efficacy and safety with generic products.

From the three products compared with Tegretol in this study only product A is not bioequivalent with the reference product with respect to the extent of absorption (Table 4). The extent of absorption of products B and C are well within the range of acceptance (0.8–1.20) for bioequivalence.

With respect to the C_{max} values, however, none of the test products is bioequivalent with Tegretol as the 90% confidence intervals are out of the range of 0.75–1.35. From these results one can conclude, that based on the observed C_{max} values, the rates of dissolution and absorption of carbamazepine from the four products studied can be ranged in the order $A < D < B < C$ (see also Figure 3). The conclusion can be drawn that products B and C are bioequivalent with each other but not with D and that product A is bioinequivalent with all three other products after single-dose administration.

The side effects measured in the volunteers after exposure to the four products (Table 3) show the same pattern for the total events as for the order of alteration of the C_{max} values. However, it is not possible to show a statistically significantly difference between the products with respect to the total events of side effects. With respect to dizziness products A and D showed lower occurrence of dizziness than both other products with larger rates of absorption. In healthy volunteers this side effect seems to be related to the rate of absorption as was also found by Neuvonen [7]. According to the current rules and knowledge with respect to the rate of absorption and the possibility of occurrence of side effects, registration of these products would not be granted on the basis of this type of study.

The metabolites measured in this study show the same rate and extent of exposure (C_{max} and AUC) as the corresponding carbamazepine. From the results of this study with a single dose in healthy volunteers no conclusions can be drawn about the question of whether the rate of absorption of carbamazepine from the products administered or the rate and extent of appearance of the metabolites in the systemic circulation are responsible for the side effects. From Table 1 and Figure 2 we can

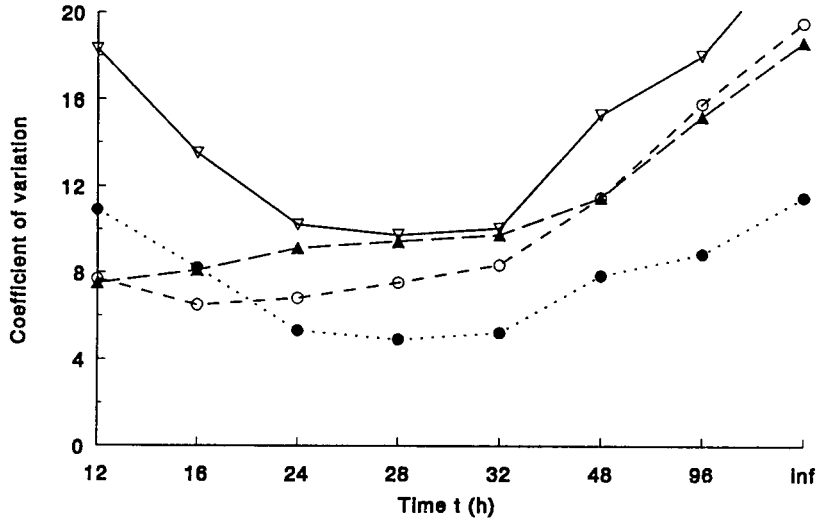

Figure 4. Coefficients of variation in C_{max}/AUC_{part} in relation with the part. AUC_{0-t} after administration of 400 mg carbamazepine to 16 healthy volunteers as four different products: ▽, product A; ○, product B; ▲, product C; ●, product D

Table 3. Occurrence of side effects after administration of 400 mg carbamazepine as four different products in 16 healthy volunteers

	Product A		Product B		Product C		Product D	
	Clearly	Weakly	Clearly	Weakly	Clearly	Weakly	Clearly	Weakly
Headache	2	1	0	1	1	1	2	0
Dizziness	1	2	6	4	7	5	1	4
Ataxia	0	0	0	1	0	3	0	1
Diplopia	1	0	1	2	1	1	0	0
Fatigue	4	3	4	6	6	0	6	2
Drowsiness	4	4	6	4	6	2	2	4
Nausea	1	0	0	0	0	4	0	0
Abdominal pain	0	0	0	0	0	0	1	0
Total events	14	10	17	18	21	16	12	11

conclude that after a single dose, the metabolites of carbamazepine do not give any additional information about differences in absorption rate between the products. Statistical testing of the AUC and C_{max} of the metabolites reveals results similar to those obtained with carbamazepine (data not shown). The ratios of the concentration of carbamazepine and those of the epoxide metabolite at the sampling time points are constant from 20 h after administration. The concentration of the epoxide is about 11 times lower and there is no difference between the products. In patients in steady-state the exposure to the epoxide may [25] or may not [26] play a role in the occurrence of side effects. In healthy volunteers, however, this will not be the case as the exposure to the metabolites of carbamazepine is dependent on the rate of absorption of carbamazepine and not on the rate of biotransformation which will be different in epileptic patients under steady-state conditions. This can be concluded from the long apparent half-life of carbamazepine-epoxide found in this study (35 h) compared with the intrinsic half-life of 6 h found by Pisani *et al*. [27] after administration of the epoxide alone.

The questions of concern are: should one use C_{max} as the measure for the rate of absorption, are other pharmacokinetic characteristics, such as partial AUC [14] or C_{max} divided by a partial AUC (AUC_{part}) [15,28] more suitable, or should we apply models for estimating the rate of absorption [29].

When applying these methods on the data from this study we see from Table 1 in which the pharmacokinetic characteristics of an open two-compartment model are listed, compared with the non-compartmental values that the AUC and C_{max} values and the variabilities are comparable, indicating that the protocol used in this study, especially with respect to the time points of sampling, was adequate for estimating the bioavailability for bioequivalence testing. The absorption half-lives estimated by the open two-compartment model are variable with very high coefficients of variation (100% or more), which is also reflected by the calculated MRT_{abs}. This method does not seem to be superior to the estimation of the pharmacokinetic characteristics using non-compartmental methods. Also the model postulated by Kayali *et al*. [30] has the same variability as the absorption rate constant. These findings are in agreement with Chen [14] who stated that the absorption rate constant alone cannot be used for comparison as it is only a parameter of rate shape and not correlated with the magnitude of absorption.

For bioequivalence testing of the rate of absorption, the partial AUC seems to have the same disadvantages as C_{max}. When the different partial AUCs

Table 4. Statistically testing for bioequivalence of $AUC_{0-\infty}$ and C_{max} ratios of three carbamazepine products (A, B, C) versus the reference product Tegretol® (D) after administration of 400 mg as a single dose to 16 volunteers

	AUC			C_{max}		
Test versus reference	A versus D	B versus D	C versus D	A versus D	B versus D	C versus D
Mean ratio (test/reference)	0.82	0.97	0.99	0.70	1.23	1.34
Range	0.45–1.60	0.35–1.49	0.83–1.17	0.40–1.40	0.21–2.03	0.66–1.86
Residual coefficient of variation		19.5%			28.5%	
F-test between products		$p > 0.05$			$p < 0.001$	
90% Confidence interval						
Paired t-test	0.73–0.92	0.86–1.09	0.88–1.09	0.60–0.83	1.04–1.46	1.13–1.58
Non-parametric	0.75–0.91	0.96–1.09	0.93–1.03	0.62–0.80	1.26–1.44	1.30–1.46

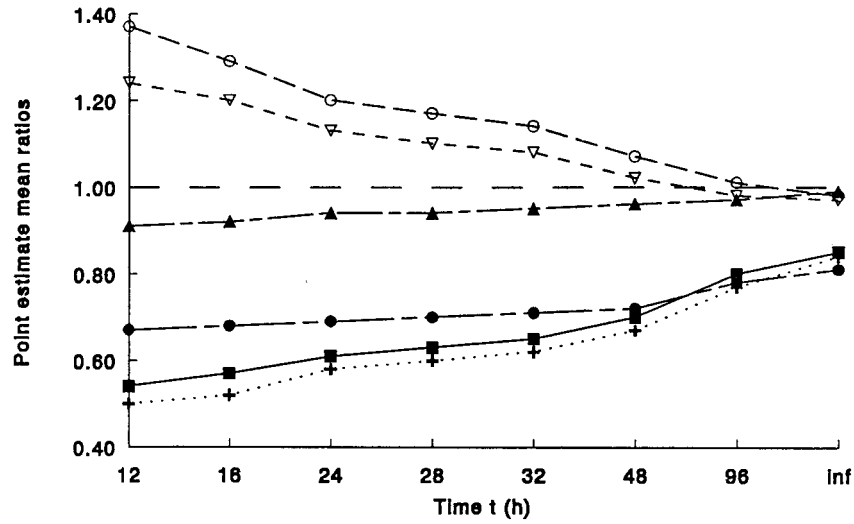

Figure 5. Point estimates of the ratios of the partial AUC in relation with the time point t of the part. AUC_{0-t} after statistical testing of the four products investigated: ●, A versus D; ▽, B versus D; ○, C versus D; +, A versus C; ▲, B versus C; ■, A versus B

for all possible combinations of comparison from this study were tested it was observed that the mean point estimates converged to 1.00 (Figure 5) and the residual coefficient of variation decreased with increasing AUC (data not shown). It seems that lower partial AUC values are more discriminating than the higher ones, and reflect better the differences found in the occurrence of side effects, especially dizziness (see Table 3). Routine use of the partial AUC as a measure for bioequivalence testing of the rate of absorption, cannot be recommended without further study of this parameter. In particular, setting the goalpost of this characteristic will be dependent on the partial AUC that will be taken into account. That the goalpost can be relaxed as suggested by Chen [14] will be dependent on the rate of absorption and the AUC taken. It is unlikely that this approach can be used, as generalization will be very difficult if not impossible.

More promising is the C_{max}/AUC_{part} measure as this metric may be more useful in the assessment of k_a [31–33] and should be independent of the extent of absorption [13,15,34]. The use of this metric and/or the C_{max} should be based on clinical usefulness [33] especially with respect to safety and the quality aspects of bioequivalence testing [35].

From investigation of this characteristic of absorption one can see (Figure 4) that the variability has a minimum between 28 and 32 h after administration, well after t_{max}, suggesting that the best estimate of this characteristic can be taken directly after completion of the absorption process. Endreny and Yan [15] suggested that under most conditions the variation of C_{max}/AUC_{part} was 10–25% higher than that of the AUC. In the present study, however, a much smaller (5–10%) variability was observed in C_{max}/AUC_{part} than for the AUCs of the same products (18–29%). When this C_{max}/AUC_{part} is

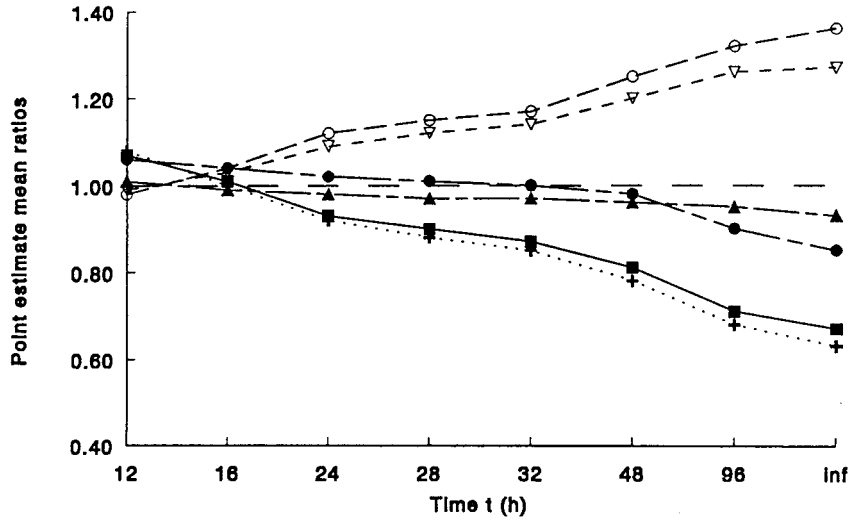

Figure 6. Point estimates of the ratios of C_{max}/AUC_{part} in relation with the time point t of the part. AUC_{0-t} after statistical testing of the four products investigated: ●, A versus D; ▽, B versus D; ○, C versus D; +, A versus C; ▲, B versus C; ■, A versus B

used to test statistically for bioequivalence one can see a development of the point estimates with a tendency opposite to the partial AUC (Figure 6). Here the lower C_{max}/AUC_{part} values are not discriminating. If this characteristic is to be used for bioequivalence testing, and for explaining the differences in side effects between the products, the partial AUC after completion of the absorption process should be taken. In the case of carbamazepine after single-dose administration this should be AUC_{32h} or later. The 90% confidence intervals of these characteristics shows that with the boundaries normally used for the extent of absorption in bioequivalence testing (0.8–1.25), all products are bioequivalent with each other and that the range of the confidence intervals is in all cases 10–12% of the mean of the reference product. Even for the two products with the large difference in dissolution rate *in vitro* (A and B) we see that for drawing the conclusion of bioinequivalence for these two products the goalpost for the 90% confidence interval should be set very narrow for partial AUC values up to 32 h. The C_{max}/AUC_{∞} seems to be more discriminating but the difference between this value and C_{max} alone is small in this case, as most of the differences in extent of absorption between the products are small. The question is then: what does one really gain with this approach? In our opinion for every chemical substance, one could develop, depending on the intrinsic pharmacokinetic characteristics, a parameter for bioequivalence with its own boundaries for bioequivalence of the 90% confidence intervals. Such an approach is unlikely to be used in routine bioequivalence testing for the registration of generic products [36]. For adoption of new metrics for bioequivalence testing, consensus on these metrics and on the objective, clinical or quality control aspects, of bioequivalence should be reached [31,35] first. As long as no other pharmacokinetic characteristic is validated C_{max} should be the characteristic of choice for the rate of absorption in single-dose studies with carbamazepine products.

Conclusions

The qualitative differences in the *in vitro* dissolution rates of the four products investigated were in the same order as the *in vivo* absorption rates after administration of the products to healthy volunteers. *In vivo*, the differences found in absorption rate were reflected in the occurrence of side effects, especially dizziness.

The metabolites, carbamazepine-10,11-epoxide and 10,11-hydroxy-carbamazepine did not give any additional information on bioequivalence or occurrence of side effects after single-dose administration.

As a measure for the rate of absorption, the partial AUC did not seem to be a good characteristic to test bioequivalence, as the variability was very high and dependent on the AUC taken. The boundaries of the 90% confidence interval for bioequivalence are dependent on the partial AUC taken and probably are dependent also on the intrinsic rate of absorption.

The C_{max}/AUC_{part} seems more promising, especially if one takes the partial AUC directly after completion of the absorption process. The variability is then low in the case of carbamazepine after a single dose but the boundaries of the 90% confidence interval will be narrow and difficult to define.

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