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Pharmacokinetics and cognitive effects of carbamazepine formulations with different dissolution rates

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Abstract *Objective*: In this study our aim was to assess pharmacokinetic effects and adverse cognitive effects of switches between generic and branded formulations of carbamazepine (CBZ).
Method: Twelve patients were included in a randomized open-label, observer-blind, cross-over design with a double-baseline period, comparing three different formulations of carbamazepine in monotherapy – the innovatory branded form Tegretol and two generic forms, CBZ Pharmachemie and CBZ Pharbita. Cognitive assessment was carried out at baseline and 3 days after a cross-over.
Results: Area under the curve and a number of pharmacokinetic properties (serum concentration day curves, change in serum concentration (delta scores), peak/trough concentrations and peak time) did not differ among the three CBZ formulations. Therefore, the basic assumption for this study, i.e. to test pharmacokinetic-related differences in cognitive profile, was not met. In line with these findings, none of the cognitive variables showed statistically significant differences with respect to the cognitive profile during the day.
Conclusion: Switches between the investigated generic CBZ formulations and the branded product did not result in any difference in cognitive profiles. These results are not necessarily valid, though, for other generic forms of CBZ, for other types of antiepileptic drugs or for CBZ treatment in higher doses or in polytherapy.

Key words Carbamazepine, Generic formulations

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Introduction

Governmental health policy in many countries worldwide is to encourage prescribing of generics as an alternative to the branded drug. Economic considerations are the major drive behind this policy. The Drug and Therapeutic Bulletin recommended generic prescribing of antiepileptic drugs (AEDs) as early as 1987, despite serious concern about the effect of changes from branded drugs to generics on seizure control efficacy. Differences between generic and branded AEDs have been studied extensively since then. A study in the UK, for example, did not find differences between the branded form of carbamazepine (CBZ; Tegretol) and generic forms of CBZ with respect to bioavailability or serum concentration day curves [17]. In addition, long-term follow-up of treatment with CBZ, in which several switches occurred, did not give rise to a significant loss in efficacy [18]. In contrast, other studies found differences in pharmacokinetics, bioavailability and seizure control efficacy in favour of branded formulations [10, 16, 19, 27]. Nonetheless the American Federal Drug Administration regards generics as an acceptable alternative for branded drugs, even allowing a plus or minus 20% difference in bioavailability [29]. The European guidelines allow similar deviations [15]. Consequently, generic prescribing of AEDs has more than doubled during the last 5 years [9].

An unsolved issue is the effect of switches between branded and generic forms of AEDs on safety and tolerability. This became a serious topic of debate after the report in 1968 on an "epidemic" outbreak of phenytoin intoxication in an Australian city in patients who had received the drug from a manufacturer different to the usual one [31]. A recent study investigated clinical symptoms related to tolerability of CBZ. This study reported patient complaints in approximately 10% of the patients who switched from one form of CBZ product to another [10]. A specific aspect of tolerability is the development of CNS-related adverse cognitive

effects [22, 23, 30, 32]. Adverse cognitive effects of AEDs have been observed to affect daily life functioning through their impact on critical functions, such as the ability to learn in children or memory in elderly [4].

This study aimed to assess the effects of different CBZ products (branded versus generics) on cognitive function. CBZ was used in this study as it is one of the most frequently prescribed antiepileptic drugs worldwide. The branded form of CBZ (Tegretol) was compared with two generic products (CBZ Pharbita and CBZ Pharmachemie). The in vitro dissolution rates of all three products were previously studied, and the related absorption rates were studied in vivo in healthy volunteers in the Laboratory of Drug Exposure Assessment [24]. Both generics appeared to have significantly faster dissolution and absorption rates compared with the branded formulation.

Our research hypothesis, based on previous studies [14, 25], is that the rate of change in serum concentration, possibly related to the rate of absorption, may explain for the side effects that have been found in healthy volunteers [24] i.e. generics will have more side effects than the branded formulation. This hypothesis has gained validity in clinical studies which show a more favourable profile for slow-release formulations of CBZ than for regular formulations [1].

Method

Design

The study had a randomized open-label, observer-blind, cross-over design. Three different formulations of CBZ in monotherapy were compared: the innovatory branded form Tegretol (batch 190400/12637) and two generic forms, CBZ Pharmachemie (batch 95/15KB) and CBZ Pharbita (batch IC 5277 95F12). All tablets were independently controlled by the Laboratory of Drug Exposure Assessment of the National Institute for Public Health and Environment, using the United States Pharmacopeia (USP) method. The paddle apparatus were operated at 75 rpm. The dissolution medium was 900 ml 1% sodium lauryl sulphate in water at 37.0 °C ± 0.5 °C. Concentrations of CBZ were determined by UV absorbance measurement at 285 nm. Tablets were compliant with the Pharmac. European norms: all tablets contained CBZ within the limits of 95%–105%. CBZ Pharbita and CBZ Pharmachemie have a similar dissolution profile (100% at approx. 40 min), which is considerably faster than found for the Tegretol tablets (100% at approx. 80 min).

Baseline treatments. During baseline, all patients were given a branded form of CBZ, Tegretol controlled release (Tegretol-CR, Ciba-Geigy) to avoid differences in expectations during baseline assessments. Tegretol-CR compared to regular formulations of CBZ has, however, a different (i.e. slow-release) pattern of absorption and may therefore influence the results after a switch. Therefore a double baseline was used. All patients were maintained on Tegretol-CR for 8 days (baseline A). During this period all baseline assessments were carried out. On the 8th day a switch was made to one of the three CBZ formulations that were included in this study (the branded formulation Tegretol or one of the two generic forms of CBZ, Pharbita or Pharmachemie) and this was continued for 7 days (baseline B). In baseline B cognitive tests were repeated to reduce retesting effects. After baseline B, three cross-overs were carried out.

Cross-over. A cross-over to another product may result in cognitive side effects that may, however, be caused by the pharmacokinetic properties of the product itself or by the switch from the former product. Product B, e.g., may result in cognitive side effects if given after product C but not if given after product A. We therefore used a semi-randomized cross-over to guarantee that all different switches (a → b, a → c, b → c, etc.) were made. After a cross-over, a product was given for 3 days. At day 3 the cognitive assessments were carried out. The design is presented in the following schedule:

During the study two baseline and three experimental cognitive assessments were scheduled, each on the last day of the respective periods. During days 18, 21 and 24 of the study the patients were admitted to hospital. Sleeping time, meals and daily living patterns were standardized for all patients. During these days a blood sample was taken once before the drug was given (before 8.00 a.m.) and eight times after it was given: at 0900, 1000, 1100, 1300, 1400, 1500, 1600 and 2000 hours. Cognitive tests were carried out seven times during the day: 0900, 1000, 1100, 1300, 1400, 1500 and 1600 hours.

Statistics (sample size Included)

To obtain an estimate of the required sample size, a power analysis was carried out using three parameters, i.e. effect size (the expected magnitude of the differences for a critical variable), type 1 (α) error (the level of significance) and type 2 (β) error (the discriminant power) as primary factors. The effect size was set to a magnitude that is generally considered clinically relevant (see e.g. [4, 22] for a discussion). The results of one of the cognitive tests, i.e. computerized visual searching task, which has been proven to be a sensitive instrument for detecting clinical relevant adverse effects of AEDs [1, 3] and also appeared to be correlated to effects of changes in

	Basline →		Experimental phase →		
Nr patient	Baseline A duration: 8 days	Baseline B duration: 7 days	1st cross-over duration: 3 days	2nd cross-over duration: 3 days	3rd cross-over duration: 3 days
cognitive assessment →	× day 8	× day 7	× day 3	× day 3	× day 3
1 (7)	Tegretol-CR	A	B	C	A
2 (8)	Tegretol-CR	B	C	A	B
3 (9)	Tegretol-CR	C	A	B	C
4 (10)	Tegretol-CR	A	C	B	A
5 (11)	Tegretol-CR	B	A	C	B
6 (12)	Tegretol-CR	C	B	A	C

A, CBZ Tegretol (branded form of CBZ); B, CBZ Pharbita (generic form of CBZ); C, CBZ Pharmachemie (generic form of CBZ)

serum concentrations of CBZ [28] was used to estimate the effect size. For this test an effect size of 1.8 standard-deviation was found (AED induced adverse effects versus no adverse effects), with a mean of 11 ± 2.4 s. Significance level (type 1 error; α) was set at 5% (two-sided testing). The discriminative power of the tests appears to be 80% (type 2 error (β) of 20%). In the power calculation the following parameters were then introduced: (1) effect size parameter 1.8 sd. (mean 11 ± 2.4 s); (2) α of 5%; (3) β of 0.80. This yields a sample size of 12 patients in a cross-over design. Differences between the three CBZ formulations and within each group over time were tested with repeated measurement multivariate analysis of variance (MANOVA). Correlations with serum concentrations were analysed using analysis of covariance (ANCOVA) with serum concentrations of the same or the previous hours (and changes in serum concentration) as covariate.

Patients

Patients were eligible for this study if they had an established diagnosis of epilepsy with well-documented epileptic seizures and were under steady-state monotherapy treatment with at least 600 mg per day CBZ for a period of > 2 months. Only outpatients were selected. Intelligence had to be average and age had to be between 18 and 60 years. Patients were excluded if they had a psychiatric history, concomitant medical conditions (such as organic heart diseases; known liver, kidney and thyroid disorders; respiratory disorders; abnormal haematological findings; neurological deficits other than epilepsy) or used neuroactive compounds other than AEDs (psychotropic drugs, neuroleptics, antidepressants, including antihistamines, soft or hard drugs, alcohol consumption of > 3 units per day). Fourteen patients were selected by their neurologists. Two patients did not enter the study (one because of a holiday and one because of travelling distance). The remaining patients fulfilled the selection criteria, gave informed consent and entered the study. None of the 12 selected patients dropped out during the study or withdrew consent.

Table 1 gives the patient characteristics. Gender was almost equally divided. All patients were on steady-state CBZ treatment with rather long duration (an average of > 4 years before entering the study). The total daily dose ranged from 600 to 1200 mg per day. The recommended therapeutic concentration range for CBZ is 4–10 mg/l [13, 21], and Table 1 shows that all patients were being treated in the assumed therapeutic range. Most cases were classified as localized (focal/partial) epilepsies with an average duration of the epilepsy ranging from 12 to 600 months (an average of > 14 years). Such cases are representative of patients with chronic epilepsy who are referred to specialized epilepsy care.

Seizure type was classified as partial seizures (complex or simple, with or without secondary generalisation) for all patients. Most (9/12) patients were, however, seizure free during the last 6 months before the trial. Three patients suffered from simple partial seizures, varying from 1 seizure per 2 months to 2 seizures per month. One patient also had one complex partial seizure during the last 6 months preceding the trial. All patients except one remained seizure free during the study period. One patient reported two simple partial seizures during the study. Thus, although the patients suffer from a chronic epilepsy, the seizure frequency did not constitute a major interfering factor in this study.

The EEG findings were in line with the epilepsy diagnosis and showed focal epileptiform activity in the majority of the cases. Two personality factors were controlled using a Dutch modification of the Maudsley personality inventory: The Amsterdamse Biografische Vragenlijst), neuroticism (emotional lability) and somatic/neurotic complaints, as both factors may have an impact on compliance and complaint behaviour. Both scales did not show elevated levels (> 7 on these scales). Physical examination (i.e. pulse rate, blood pressure, body weight and respiratory rate) did not reveal values in the abnormal range. None of the patients had neurological abnormalities, other than epilepsy, or physical abnormalities. Most patients are non-smokers or moderate smokers and the use of alcohol was reported to be moderate. The average sleeping duration per night was rated as normal for most patients.

Cognitive tests

The cognitive tests were directed towards the cognitive domains of speed (assessing possible motor and mental slowing), short-term memory and attention/mental flexibility. Several consensus meetings have established these areas to be the critical areas of possible drug-induced cognitive impairment [12]. The cognitive domains were assessed with the "FePsy" computerized neuropsychological test battery. Test presentation and response registration was controlled by a microcomputer; however, the test procedure was always fully managed by a trained test technician. The test programme is amply discussed elsewhere [7, 8]. From this system, the tests used in earlier cognitive drug studies [1, 2, 3] were selected. In addition, a standardized rating list to evaluate subjective patient complaints (neurotoxicity scale) was used.

Speed measures

- *The finger tapping task* measures motor speed and motor fluency in five consecutive trials for the index finger of the dominant hand. Variable VI is the average number of taps for 5 consecutive trials during 10 seconds.
- *Simple reaction-time* measurement with visual stimuli (a white square on the screen) that were presented at random intervals by the computer. This test measures activation/alertness, and a strong "motor speed" component is involved. Variable V2 is the average reaction speed in milliseconds for 30 trials for the dominant hand.

Mental speed/attention

- *Binary choice reaction test*. In this test a decision component is introduced in the reaction-time measurements. The patient has to react differentially to a red square presented on the left side of the screen and to a green square presented on the right side. Reaction time here reflects not only motor speed but also the decision making process ('mental speed'). Variable V3 is the average reaction speed in milliseconds for 60 trials using a trade-off for errors.
- *The computerized visual searching task* (CVST), an adaptation of Goldstein's visual searching task. A centred grid pattern has to be compared with 24 surrounding patterns, one of which is identical to the target pattern. The tests consists of 24 trials and gives an indication of the speed of information processing and perceptual mental strategies. Variable V4 is the average searching time in seconds.

Short-term memory function

- *Recognition task*. Six words are presented simultaneously during a learning phase with a presentation time of 1 s per item. After a delay of 2 s the screen shows one of these words between distracters. The target item has to be recognized. Variable V5 is the total number of correct responses out of 24.

Subjective complaints about cognitive side effects

- *The A-B neurotoxicity scale* was used [4, 6]. This 24-item scale has proven sufficient reliability and validity in establishing patient-based cognitive complaints in relation to drug treatment. Variable V6 is the total score which ranges from 0–72 (score 3 on all 24 items).

Variables V1 to V5 are the primary cognitive variables. Variable V6 is used to control for subjective experiences.

Analysis of serum samples

In plasma, carbamazepine, carbamazepine-10,11-epoxide and 10,11-dihydroxy carbamazepine (DHC) were determined according to the following method. In short, 0.2 ml plasma samples were extracted with 8 ml dichloromethane after adding dihydrocarbamazepine as internal standard. After evaporation of the organic phase, the residue was redissolved in 0.2 ml mobile phase and 20 µl

Table 1 Demographic and clinical characteristics of the study group

Male/female	7/5 (58.3% male)
Age	45.1 ± 10.6 years
Duration of epilepsy	178.4 ± 193 months
Dose of CBZ	717 ± 180 mg·day
Duration of CBZ treatment	52.3 ± 40.9 months
Serum concentration	
– Carbamazepine	6.44 ± 1.2
– Epoxide	0.86 ± 0.32
– DHC	1.68 ± 0.75
Epilepsy diagnosis	
– Generalised epilepsy	1 patient
– Localization related (focal) cryptogenic	9 patients
– Localization related (focal) symptomatic	2 patients
Seizure types	
– Simple/complex partial	4 patients
– Simple/complex partial + secondary generalisation	8 patients
EEG findings	
– Generalised epileptiform activity	1 patient
– Focal activity	9 patients
– Multifocal activity	2 patients
Aetiology	
– Unknown	4 patients
– Traumata	6 patients
– Other	2 patients
MRI/CT	
– Normal	10 patients
– Abnormal	2 patients
(1 AVM; 1 left ventricle enhanced)	
Intelligence (Raven IQ)	115.4 ± 15.3
Neuroticism (ABV–N Score)	6.0 ± 2.8 (stanines)
Somaticism (ABV–NS score)	4.8 ± 2.9 (stanines)
Weight	88.0 ± 27.8 kg
Height	170.9 ± 27.9 cm
Pulse rate	71.8 ± 9.3 p·min
Blood pressure	
– Systolic	135 ± 10.9
– Diastolic	85.4 ± 7.8
Respiratory rate	14.1 ± 1.6 min
Neurological examination	
– No abnormalities	All patients
Physical examination	
– No abnormalities	9 patients
– Abnormalities	3 patients
(asymmetrical face/skull; exostoses on right hand; haematinic right upper arm)	
Smoking	5 patients (moderate)
Alcohol	8 patients (< 1 unit per day)
Sleep	7.5 ± 1.1 per night

was injected in the HPLC system with a Hypersil MOS 5-μm column (100 × 4.6 mm). The mobile phase consisted of methanol–acetonitrile–Sörensen buffer (pH 7.0:25:10:65 v/v). The method was validated for all three components. The limit of quantitation of all three compounds was 0.02 mg/l plasma. The method was linear over the range of 0.05–12 mg/l plasma and the imprecision was less than 2%. The pharmacokinetic variables were calculated model-independently with the program TopFit. The area's under the plasma concentration time curves were calculated with the linear trapezoidal rule. The maximum plasma concentration (O_{max}) and time to reach maximum plasma concentration (t_{max}) were obtained directly from the plasma concentration/time data.

The study was approved by the Scientific Board of Epilepsy Centre Kempenhaeghe and by the Medical Ethics Committee. All patients gave written informed consent.

Results

Baseline measurements

Table 2 shows the results of cognitive assessments during baseline A (Tegretol controlled release for all patients) and baseline B. Comparison between both assessments shows that none of the tests gave rise to significant retesting effects. When these results are compared with the norms for these tests [2, 3, 7, 8] the patients perform in accordance with the average performance level in patients with epilepsy. The subjective

Table 2 Cognitive baseline scores during baseline A (Tegretol-CR) and baseline B (one of the "experimental forms" of carbamazepine)

	Mean (SD) 1st assessment; baseline A	Mean (SD) 2nd assessment; baseline B	*t*	*P*
1. Finger tapping dominant hand	61.2 (5.7)	62.8 (7.3)	−1.39	0.19
2. Visual reaction time	292.8 (41.8)	273.8 (41.4)	1.64	0.13
3. Binary choice reaction time	405.3 (68.7)	384.9 (74.4)	1.13	0.28
4. Visual searching task	12.4 (3.9)	11.5 (3.9)	1.18	0.26
5. Recognition task	18.9 (3.5)	19.2 (2.9)	−0.39	0.74
6. Neurotoxicity	8.2 (8.7)	10.3 (8.3)	−2.03	0.67

* *P* values < 0.05 are significant

complaints, as assessed with the neurotoxicity scale, reveal that most patients did not subjectively experience cognitive impairment that they associate with their drug treatment. As can be expected with subjective measurement, standard deviations are high, indicating high inter-individual variability.

Pharmacokinetics and bioavailability

Table 3 shows the main results of the serum sampling analysis during the cross-over phase: (a) serum concentration of CBZ; (b) area under the curve (AUC); bioavailability of the drug; (c) peak and trough serum concentration (C_{max} and C_{min}); (d) time of peak concentration (T_{max}). The values for carbamazepine-10,11-epoxide and 10,11-dihydroxy carbamazepine (DHC) metabolites are not given as there was no major difference between them. The serum-concentration day curves in Table 3 do not reveal large differences between the three CBZ formulations. Table 3 shows that also for the remaining pharmacokinetic values ($C_{MAX}/C_{MIN}/t_{MAX}$) and for the value of bioavailability (AUC) only moderate differences have been obtained. A statistical analysis of the serum-concentration day curves using repeated measurement MANOVA did not reveal statistically significant differences between the three products (SS/MS 1.27/0.09; *F* value 1.33; $P = 0.21$). The delta scores also do not show differences between the three CBZ formulations (repeated measurement MANOVA: SS/MS 1.02/0.09; *F* value 1.52; $P = 0.14$). Post hoc ANOVA *P*-values are included in Table 3 (last column; none of the values are significant). Note that none of these values reach statistical significance although such post hoc analyses overestimate differences. Differences in bioavailability (AUC), peak and trough concentrations (C_{MAX} and C_{MIN}), peak time (t_{MAX}) and range also do not reach statistical significance (for *P* values: see Table 3).

Cognitive test scores

The cognitive test scores (seven scores obtained during the day for each of the CBZ formulations) were statistically analysed using repeated measurement MANOVA. This yielded two types of analysis: (1) "time effect", indicating whether significant changes in cognitive function occur during the day, for all three CBZ formulations combined; (2) the interaction between time-effect and type of CBZ formulation (Tegretol versus Pharbita versus Pharmachemie), indicating whether statistically significant differences in cognitive function occur during the day between the three different CBZ products (Tegretol versus Pharbita versus Pharmachemie). Table 4 gives the mean scores and the results of statistical testing. For the finger tapping task no significant "time-effect" was found; this indicates a relatively stable performance over the day for the three CBZ formulations combined ($P = 0.28$). No differences were found between the three CBZ formula-

Table 3 Serum levels of CBZ, (in mg/l) AUC, peak (C_{max}) and trough (C_{min}) levels and time of peak concentration (t_{max}) for Tegretol and two generic forms of CBZ. Values given are mean (SD)

Time	Tegretol	Pharbita	Pharmachemie	*P**
0800 hours (predose)	5.84 (0.97)	6.25 (1.37)	6.08 (1.50)	0.91
0900 hours	6.77 (1.07)	7.08 (1.43)	6.59 (1.47)	0.87
1000 hours	6.95 (1.05)	7.45 (1.54)	6.84 (1.46)	0.80
1100 hours	6.99 (1.11)	7.55 (1.78)	6.95 (1.42)	0.81
1300 hours	8.04 (1.15)	8.37 (2.11)	7.45 (1.17)	0.70
1400 hours	8.13 (1.15)	8.56 (2.01)	7.82 (1.42)	0.80
1500 hours	8.06 (0.98)	8.48 (1.98)	7.98 (1.56)	0.89
1600 hours	7.78 (1.03)	8.11 (1.90)	7.89 (1.60)	0.96
2000 hours	6.56 (1.04)	7.02 (1.35)	6.94 (1.56)	0.88
AUC	87.98 (12.51)	92.90 (20.84)	87.52 (17.54)	0.89
C_{max}	8.28 (1.1)	8.67 (1.96)	8.17 (1.55)	0.90
C_{min}	5.84 (0.97)	6.25 (1.37)	6.06 (1.47)	0.91
t_{max}	13.83 (0.58)	14.25 (0.42)	14.83 (0.58)	0.07
Range	2.44 (0.18)	2.42 (0.65)	2.11 (0.22)	0.47

* *P* values indicate nonsignificance (all values > 0.05)

Table 4 Repeated measurement MANOVA for the cognitive test scores

Cognitive tests	Scores at 0915, 1015, 1115, 1315, 1415, 1515, 1615 hours[a]	"Time effect"[b] (repeated measurement MANOVA)	Interaction[c] between "time effect" and type of CBZ formulation
Finger tapping (number of taps)	*Tegretol*: 66.1(8.3); 68.5(8.1); 68.5(8.7); 67.3(9.3); 68.4(8.6); 68.1(8.1); 67.7(8.7); *Pharbita*: 62.0(3.4); 62.4(3.4); 62.5(3.6); 62.6(3.6); 61.3(3.7); 61.8(2.7); 62.5(3.6); *Pharmachemie*: 65.7(6.1); 65.8(8.0); 66.2(7.4); 65.4(8.1); 64.6(8.5); 65.1(8.3); 64.8(8.2)	SS/MS 11.90/1.98; *F* value 1.41; $P = 0.28$ (NS)	SS/MS 19.43/1.62; *F* value 1.15; $P = 0.43$ (NS)
Visual reaction time (ms)	*Tegretol*: 277.3(23.1); 271.7(32.8); 274.6(38.8); 271.1(24.9); 280.6(47.7); 286.9(51.8); 274.0(36.4) *Pharbita*: 274.7(56.1); 291.7(43.1); 294.5(51.7); 302.2(52.4); 301.1(46.1); 296.2(57.9); 287.1(47.6) *Pharmachemie*: 291.8(53.0); 297.1(59.3); 294.3(67.6); 299.4(66.4); 300.1(60.7); 308.5(85.6); 312.0(76.0)	SS/MS 1929.0/321.5; *F* value 1.51; $P = 0.19$ (NS)	SS/MS 2237.45/186.45; *F* value 1.51; $P = 0.57$ (NS)
Binary choice reaction time (ms)	*Tegretol*: 336.0(52.4); 342.3(44.6); 345.0(49.0); 332.5(62.3); 348.4(45.7); 352.5(64.2); 364.1(41.5) *Pharbita*: 363.0(45.9); 361.6(45.4); 370.9(40.8); 375.6(30.7); 374.1(60.2); 371.9(28.9); 384.9(44.3) *Pharmachemie*: 383.1(37.8); 397.0(36.9); 411.3(49.0); 402.5(50.1); 406.5(61.2); 399.2(47.2); 415.5(58.3)	SS/MS 5345/890.98; *F* value 3.83; $P = 0.003^{**}$	SS/MS 1551.86/129.3; *F* value 0.56; $P = 0.86$ (NS)
Visual searching task (s)	*Tegretol*: 9.5(1.7); 9.6(2.0); 8.6(1.4); 9.1(2.5); 8.4(1.8); 9.3(2.4); 9.3(1.9) *Pharbita*: 9.9(4.6); 8.7(3.2); 8.3(2.9); 9.0(3.7); 9.7(5.2); 8.6(3.6); 7.8(3.6) *Pharmachemie*: 9.0(1.7); 8.4(2.1); 7.9(2.6); 7.8(2.1); 7.5(2.4); 8.0(1.7); 7.5(2.0)	SS/MS 13.86/2.31; *F* value 2.86; $P = 0.002^{**}$	SS/MS 12.84/1.07; *F* value 1.42; $P = 0.18$ (NS)
Recognition task (number correct out of 24)	*Tegretol*: 20.4(1.3); 20.5(0.4); 20.4(1.9); 21.4(1.6); 20.1(2.1); 20.8(2.6); 20.2(1.5) *Pharbita*: 18.7(2.6); 19.1(3.1); 18.5(4.5); 18.8(3.2); 20.3(2.3); 19.1(2.4); 19.7(2.1) *Pharmachemie*: 19.6(4.4); 20.3(4.1); 20.2(3.6); 20.4(3.0); 20.8(3.3); 19.9(3.2); 20.4(3.2)	SS/MS 5.94/0.99; *F* value 0.84; $P = 0.54$ (NS)	SS/MS 11.20/0.93; *F* value 0.79; $P = 0.66$ (NS)

NS not significant

* Significant *P* values < 0.05

** Significant *P* values < 0.01

[a] Values given are mean (SD)

[b] "Time-effect" indicates fluctuations in cognitive performance during the day for all three CBZ formulations

[c] "Interaction" indicates differences in cognitive fluctuations between the three drug formulations (Tegretol versus Pharbita versus Pharmachemie)

tions during the day ($P = 0.43$). Statistical testing for simple visual reaction-time measurement did not yield a significant time effect ($P = 0.19$) and no differences between the three CBZ-formulations ($P = 0.57$). For binary choice reaction time test a significant time-effect ($P = 0.003$) was found, caused by fluctuations during the day without a consistent pattern. The interaction between time-effect and type of CBZ formulation is not significant ($P = 0.86$); hence, no differences were found between the three CBZ formulations. For the computerized visual searching task, statistical testing yielded a significant time-effect ($P = 0.002$), caused by the increase in speed during the day for this task, possibly caused by a ''learning effect''. There were no differences between the three CBZ formulations ($P = 0.18$). For the recognition test no significant time-effect ($P = 0.54$) and no differences between type of CBZ formulation ($P = 0.66$) were found.

Correlations between cognitive test scores and serum concentrations

Performance was also analysed for possible correlations between cognitive test scores and serum concentration/change of serum concentration (delta). This analysis was performed using ANCOVA (analysis of covariance) for differences between the CBZ-formulations with serum concentrations (or delta) as covariate. None of the correlations were statistically significant.

Subjective complaints about cognitive side effects

In contrast to the primary cognitive test variables, the neurotoxicity scale was only used once a day. The scores were Tegretol 6.75 (SD 5.6); Pharbita 2.92 (SD 2.7); Pharmachemie 13.8 (SD 12.8). Inspection of the result per patient, however, reveals large inter-individual variability as also illustrated by the high standard deviations (that were already observed during baseline). The results were statistically analysed with ANOVA, and no significant differences were revealed (F value 1.796; $P = 0.22$).

Conclusion

The general conclusion of our study is that the differences between the three CBZ formulations (one branded and two generic forms) are relatively small with respect to bioavailability (AUC) and a number of pharmacokinetic properties (serum-concentration day curves, change in serum concentrations as expressed in delta scores, peak/trough concentrations and peak time). By and large, the three CBZ formulations can be considered as equivalent in terms of investigated pharmacokinetic properties under steady-state condition. Therefore the basic goal of this study, i.e. to test pharmacokinetic-related differences in cognitive profile could not be achieved. The focus of our study was thus limited to testing cognitive function in a bioequivalence design.

In line with these findings none of the five primary cognitive test variables show statistically significant differences between the three drug conditions. The cognitive profiles during the day coincide to a great extent. None of the explored relationships with serum concentrations or with delta scores reveal statistical correlations. The major conclusion is, therefore, that significant switches between the branded form of CBZ and the investigated generic forms of CBZ formulations do not result in different cognitive profiles.

Despite these results, it must be mentioned that four of the five cognitive test variables show better scores for the branded form of CBZ Tegretol. Although none of the comparisons in the study yielded a statistically significant difference, it may be argued that genuine differences do exist but that these difference are too small to be detected in the relatively limited sample size of 12 patients. Inspection of the differences of test scores between the products reveals, however, that for most differences the magnitude would not be considered relevant in clinical practice. Possibly a much larger sample size would reveal some statistically significant effects, but even then the obtained differences would still not permit the conclusion of ''cognitive side effect'' in clinical practice. This adds to validity of the ''no-effect finding'' of our study.

Moreover, it may be argued that we did not study the effects under steady state, as the intervals from cross-over to reassessment 3 days) was too short. However, since all patients remained on CBZ treatment with an unchanged dose throughout the study, no change in the pharmacodynamic effect is anticipated that would require longer periods of adaptation to compensate for initial adverse effects and to reach steady state. A longer interval would possibly have leveled out potential behavioural reactions to one of the products due to processes such as positive tolerance or habituation [20]. As we aimed at assessing all possible behavioural effects (a ''worse case scenario'') the 3-day interval was considered appropriate.

It may also be argued that a ''suppressing'' factor caused lowered cognitive scores that may have masked the cognitive effects of the drug. However, the results do not support this argument. The most important suppressing factor are the epileptic seizures that may have a substantial impact on cognitive function (e.g. [11]). Most (9/12) patients were, however, seizure free during the 6 months before the study and 11/12 patients remained seizure free during the study. Moreover, none of the test scores indicate such a suppressing effect. In fact all scores were in the higher range.

Some caveats for interpretation of the results of this study are required. First of all, our results cannot be generalized to other antiepileptic drugs. Carbamazepine has a specific pharmacokinetic profile and for other AEDs formulation differences may have a more severe impact on cognitive function. It may be valuable to test phenytoin and valproic acid, AEDs with entirely different pharma-

cokinetic profiles. Secondly, the results pertain to the comparison between "regular" forms of CBZ formulations. If the comparison would have included slow-release forms of CBZ formulations other results could have been obtained. Several studies, e.g. by our own research group [1] have established a relatively favourable cognitive profile for slow-release forms of CBZ compared to regular CBZ formulations (including Tegretol). Interestingly, all patients preferred CBZ controlled-release as their drug after the study was finalized, including the patients that were on other types of CBZ before the study. Thirdly, all patients were treated within the assumed therapeutic range for CBZ (range 4.6–8.4 mg^{-1}). This is representative for regular treatment with CBZ monotherapy in the majority of the patients. The results are thus representative for normal clinical practice. If treatment requires a higher dose or if CBZ is used in polytherapy the results may be different.

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