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A MULTICENTER, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF EFFICACY OF A NEW FORM OF CARBAMAZEPINE (CARBATROL^R) IN REFRACTORY EPILEPTIC PATIENTS

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A multicenter, placebo-controlled, double-blind study of efficacy of a new form of carbamazepine (Carbatrol^R) in refractory epileptic patients. W. SOBANIEC, W. KUŁAK, J. ŚMIGIELSKA-KUZIA, L. BOĆKOWSKI, J. MAJKOWSKI, J. JĘDRZEJCZAK. Pol. J. Pharmacol., 2004, 56, 195–201.

Carbatrol (CBR) is a new multiple-unit, sustained-release dosage form of carbamazepine (CBZ) developed by Pharmavene. We present a multicenter, outpatient, randomized, double-blind parallel group study (No PI 101) carried out in two centers in Poland. CBR was evaluated in 47 patients with uncontrolled partial onset seizures. During the 28-day baseline period, patients were required to have at least two seizures and to take CBZ at a therapeutic level, a second antiepileptic drug was allowed but not valproic acid (VPA). Patients were randomized to VPA or to CBR (dosages 800, 1200, 1600 mg/day). Criteria for escape relative to baseline were: two-fold increase in monthly seizure frequency, two-fold increase in 2-day seizure frequency, two-fold increase in weekly seizure frequency, single generalized tonic-clonic seizure (GTCs) if none occurred during baseline or prolongation of GTCs. The primary efficacy variable was the number of patients escaping in each treatment group. Nineteen patients on VPA and 7 on CBR met escape criteria. CBR adverse experiences were all mild or moderate in severity. CBR therapy was effective in the treatment of partial complex seizures with or without generalization.

Key words: *carbamazepine, carbatrol, uncontrolled partial seizures, epilepsy*

correspondence

Abbreviations: AED(s) – *antiepileptic drugs(s)*, CBR – *carbatrol*, CBZ – *carbamazepine*, CLZ – *clorazepate,* GTCs – *generalized tonic-clonic seizures*, PB – *phenobarbital*, PHT – *phenytoin*

INTRODUCTION

Patients with medically uncontrolled seizures present a major challenge to physicians, the health care system, and society. Despite the advent of new antiepileptic drugs (AEDs) [13, 19] still 20–30% of epileptic patients remain unsatisfactory controlled [5].

Carbamazepine (CBZ) is a the principal drug of choice for the treatment of simple or complex partial seizures and secondary generalized seizures [5, 16]. Patients with partial seizures are often poorly controlled by available and new AEDs [5].

In contrast to other AEDs, CBZ induces its own metabolism thereby enhancing its elimination and reducing its half-life from about 30 h to 10–15 h [4, 11, 16, 21]. Due to its slow and irregular absorption and to its short half-life, considerable fluctuations in the serum of CBZ and CBZ-10,11-epoxide have been observed [6, 9, 12, 14]. These fluctuations, in some patients, may result in intermittent side-effects, such as diplopia, nystagmus, ataxia, headache and dizziness [2, 3, 8, 17].

Despite drug titration and q.i.d (four times daily) dosing with CBZ, variable peak-to-trough fluctuations and adverse reactions continue to occur [8, 14, 16, 17]. Preparations with a slow release of CBZ should smooth the concentration profile and should allow an application frequency 1–2 times daily [15]. A dosage form of CBZ has been developed by Pharmavene that is designed to minimize variation in peak-to-trough levels and provide a more convenient twice a day dosage regimen for patients. The dosage form is a capsule that contains a mixture of pellets with different release characteristics. In earlier studies, the pharmacokinetics of the individual capsule components were studied in normal volunteers. Component A is an immediate release pellet, component B is a sustained-release pellet, and component C is a delayed-release pellet. Based on an evaluation of these results, a multiple pellet dosage form has been designed that contains different ratios of the three components. The objective of this study is to evaluate the safety and efficacy of this multiple-unit, sustained-release dosage form of CBZ. We present results of a multicenter, outpatient, randomized, double-blind parallel group study [No PI 101, 104] carried out in two centers in Poland.

MATERIALS and METHODS

Design of the study

The design was a 12-week multicenter, outpatient, randomized, double-blind, parallel group study in patients with psychomotor epilepsy (Fig. 1). Each patient was receiving either mono-

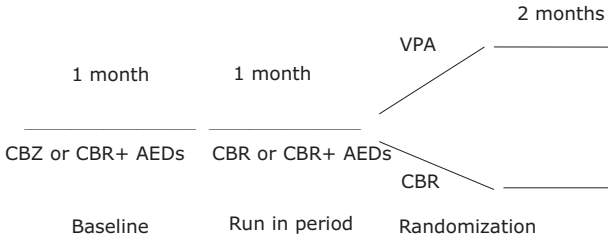

Fig. 1. Scheme of design of the study; AEDs – antiepileptic drugs, CBR – carbatrol, CBZ – carbamazepine, VPA – valproate acid

therapy with CBZ or CBZ and one another AED (but not valproic acid, VPA). The patients have been maintained on a stable dose of their standard AED therapy for at least 30 days. Twenty-five patients had CBZ monotherapy and 22 had bitherapy, details are shown in Table 2. Seven to ten days prior to entry into the study, patients have had their physical exams, clinical tests, and urine pregnancy test, where indicated. During an optional one-week period preceding the study, patients whose stable CBZ doses were not equal to one of the allowed fixed daily doses might have their CBZ doses adjusted to one of the fixed doses allowed. Patients whose daily dose was, in the investigator's judgment, reasonably close to one of the allowed fixed doses could begin the allowable fixed dose without a one-week transition. For the first 4 weeks of the study, patients received their established (fixed) daily dose of CBZ as Pharmavene's formulation Carbatrol^R (CBR) q 12 h, as well as their additional AED (if they were receiving one), and completed a seizure diary. After 4 weeks, patients have been randomized to receive either the Pharmavene formulation of CBZ q 12 h (Treatment 1) or VPA (Treatment 2) q 12 h for up to 8 weeks. The maximum daily dose of CBZ was 1600 mg, and the maximum daily dose of VPA was 1000 mg. All

doses were determined by the daily dose of CBZ with which the patient entered the study. Drug safety and efficacy were assessed by a variety of criteria.

Subject selection

Subjects were drawn from a pool of out-patient clinics of the Department of Neurology of Medical Academy in Białystok and Department of Neurology, Medical Center for Postgraduate Education in Warszawa with complex partial seizures, with or without secondary generalization. Safety was assessed by: 1) physical examination, 2) assessment of adverse reactions, 3) laboratory tests, 4) clinical evaluation. Efficacy was assessed by: 1) number of patients who completed the study and who fail to meet escape criteria, 2) time to drop-out and, including those patients who remained in the study, the time to experience three seizures.

A. Inclusion criteria were:

- males and females, 18 to 60 years of age;
- weight for height plus or minus 25%;
- patients with history of partial seizures with complex symptomatology, with or without secondary generalization with at least two seizures in the 4 weeks prior to entry into the study (not including the optional one-week dose adjustment week;
- stable CBZ dose for at least 30 days prior to enrollment. This dose might be adjusted slightly up to one week prior to study entry, but only if the stable dose was not one of the allowed fixed doses. During the first four weeks of the study, patients had to receive a fixed daily dose of CBZ equal to 800, 1200, or 1600 mg;
- patients could be given one additional AED (but not VPA) as long as doses remained stable for at least 30 days prior to study entry and throughout the study period;
- patients had to be physically healthy for their age, with no history of major chronic or debilitating illness.

B. Exclusion criteria were:

- patients with a history of sensitivity or adverse reactions to CBZ, VPA, or tricyclic antidepressants:
- patients with a significant history of heart disease;
- patients with a history of other neurological or psychiatric disorders;
- patients requiring concomitant medications which could interfere with patient compliance or study conduct, e.g. sedatives, hypnotics, antidepressants, and neuroleptics;
- patients who had clinically abnormal laboratory values;
- participation in a study with another experimental drug within 4 weeks prior to entering the study;
- patients who were currently or were known to have been abusers of alcohol, hallucinogens, or agents which were addicting within the past 6 month;
- patients with any disease of the gastrointestinal system, liver, or kidneys, or abnormal condition which compromises a function of the systems and could result in a possibility of altered absorption, excess accumulation, or impaired metabolism or excretion of the study drug;
- pregnant or lactating women or having had three or more days of amenorrhea beyond the time of expected menses at the time of the first dose of study medication.

Withdrawal criteria were: withdrawal of informed consent, severe or unacceptable adverse experiences, including hematological or biochemical abnormalities, or met escape criteria.

The protocol was approved by the Ethical Committee in both centers of the study. All patients participated on the basis of informed consent which was signed.

Procedures

On admission to the trial all patients underwent a full general physical and neurological examination together with biochemical and hematological screening and urine analysis. Patients desiring to enroll in the study and whose stable CBZ dose was not 800, 1200, or 1600 mg daily had their CBZ doses adjusted to one of these levels during a period of up to one week prior to study entry. Patients were receiving their daily fixed dose of CBZ as Pharmavene's formulation q 12 h and continued to receive any second AED (not VPA) for the first 4 weeks of the study. Their CBZ dose was equivalent to 800, 1200, or 1600 mg daily throughout this period. After this 4-week run-in period, patients continued taking their stable dose of any preexisting second AED. Patients were randomized to receive either the Pharmavene formulation of CBZ

q 12 h (Treatment 1) or VPA – sodium valproate (Treatment 2) q 12 h. Next, patients were given the assigned treatment with Pharmavene formulation CBR or VPA, depending upon the patient's entering daily dose of CBZ.

The escape criteria were defined as follows:

1. A two-fold increase in the highest 2 day seizure frequency, or two seizures in one week for patients who met inclusion criteria but nevertheless had no seizures during the first four weeks of the study.

2. A two-fold increase in weekly seizure frequency (complex partial or secondarily generalized seizures), or two seizures in two weeks for patients who met inclusion criteria but nevertheless had no seizures during the first four weeks of the study.

3. A single generalized tonic clonic seizure if generalized seizures were not present during the 4-week baseline period.

4. A prolongation of generalized seizure duration (serial seizures or status) deemed by the investigator to require intervention.

During the course of the 12 week study, every patient had to keep a seizure diary and recording the date along with the approximate length of each of seizures. During the course of the study outpatient visits were every two weeks. Physical examination was repeated as required throughout the study, but only changes were recorded except the conclusion of the study. Occurrence of adverse effects was evaluated and documented by the investigators during each visit. Patients were instructed to contact the clinic immediately if they had experienced seizures of increasing severity or frequency or they experienced serious adverse events between outpatient visits. Each control blood sample collected at pre-study and end-of-study was assayed for the following: 1) hematology – complete blood cell count, white blood cell count differential, platelet count; 2) clinical chemistry – SGPT, SGOT, albumin, alkaline phosphatase, direct bilirubin, total bilirubin, BUN, creatinine, total calcium, cholesterol, chloride, globulin, glucose, LDH, phosphorus, potassium, total protein, sodium, triglycerides and uric acid. A total CBZ concentration was assayed using Biotrack 512 – Ciba Corning. The Biotrack 512 system is an immunoassay system that measures drug concentration by a turbidimetric latex agglutination inhibition reaction [7]. The device is a self-contained unit with an opening in front for the insertion of the test cartridge or calibration cartridge. The disposable test cartridges are similar in size to a standard audio cassette and contain all the dry reagents and liquid diluents. Whole blood from fingerprick was used as samples and are deposited onto the test cartridge which is then inserted into the Biotrack. No user intervention is required following insertion of the test cartridge and results of each sample are displayed on a digital screen after approximately 3 min. Internal calibration is performed once daily by the operator, using a standard calibration cartridge.

Statistical analysis

The percentage of patients who met escape criteria in each treatment group was compared using the chi-square test with Yates' correction. Times to drop-out and time to experience three seizures were analyzed using appropriate statistical method. Laboratory findings and data on signs and symptoms reported during the trial were analyzed descriptively, laboratory values were analyzed for changes from baseline using Student's *t*-test.

RESULTS

Forty-seven patients entered the study, and 36 patients completed all 12 weeks (run- in and randomized period). Six patients were excluded from the study after 4 weeks with CBZ treatment, one due to meting escape criteria, five were uncooperative. Demographic and the disease features of the participating patients are summarized in Tables 1 and 2.

Efficacy

The two treatment groups were comparable at baseline with respect to their age, sex, height, body weight, seizure frequency during the baseline period 22.1 in the CBZ group, 11.2 in the VPA group. The baseline AEDs were administered either as single drug CBZ or co-administered with phenytoin (PHT), phenobarbital (PB) or clorazepate (CLZ) (Tab. 2). The most common AEDs in both groups was CBZ (25 patients). The mean CBZ dose was 800 mg/day in 22 patients, dose 1200 mg/day in 16 patients and 9 patients had dose of 1600 mg/day. In all patients mean CBZ dose was 1089.4 mg/day during the baseline period among all patients, and the mean dose of VPA was 730 mg/day in 24 patients during randomized period, and CBZ 1126 mg/day during the randomized period.

Table 1. Demographic data

Age (yrs)	
Range	18–52
Mean (SD)	30.8 ± 7.92
No. of	
Males	26
Females	21
Height (cm)	
Range	150–187
Mean (SD)	170.3 ± 8.66
Weight (kg)	
Range	46–103
Mean (SD)	67.4 ± 12.80

Table 2. Statistics of seizure history

Etiology of seizures	
Idiopathic/unknown	42
Symptomatic	5
Duration of seizures at entry to trial (yrs)	
Range	0.3–29
Mean (SD)	14.4 ± 9.2
Seizure counts for all patients per month	
Range	2–100
Mean (SD)	19.1 ± 24.6
Number of patients taking AEDs	
CBZ	25
CBZ+PHT	17
CBZ+PB	4
CBZ+CLZ	1

Figure 2 illustrates the outcome in the treatment groups during exposure to CBR or VPA. The patients of CBR group met escape criteria within an average of 6.5 weeks of the randomized period, whereas the patients of VPA group met these criteria within an average of 2.6 weeks of the randomized period.

There was a significant ($p < 0.01$) effect of the percentage of patients who met escape criteria in each treatment group (Tab. 3). Among the 19 CBZ-treated patients, 12 (63.1%) completed the 84 day trial, 7 (36.8%) met escape criteria. In the 23 VPA-treated patients, 4 (17.3%) patients completed the 84 day trial, 19 (82.6%) met escape criteria.

Table 3. Comparison of number of patients who completed the study with those who met escape criteria

		Completed the study	Met escape criteria	p value
CBR	n = 19	12 (63.1%)	7 (36.8%)	
VPA	n = 23	4 (17.3.%)	19 (82.6%)*	< 0.01

Chi-square test with Yates' correction * $p < 0.01$

Table 4 . Most frequently reported treatment adverse events

Nature of adverse events	Number
Central nervous system	
Headache	5
Migraine	4
Somnolence	2
Memory impairment	2
Vertigo	6
Nervousness	1
Hand tremor	1
Leg tremor	1
Gastrointestinal	
Increased appetite	3
Respiratory tract	
Cold	3
Pharyngitis	2
Bronchitis	1

Table 5. Mean plasma concentrations of carbamazepine during the baseline and after 4 weeks of treatment with carbatrol (CBR) (n = 33 patients)

	Range (μg/ml)	Mean concentrations ± SEM (μg/ml)
Baseline	2.9–14	7.28 ± 0.44
After 4 weeks of treatment with CBR	2.9–14	7.43 ± 0.51

Safety

There were changes in the mean levels of several hematological and biochemical parameters during treatment, but most of them were minor and of no clinical significance. Adverse events other than seizures during the 8-week treatment were reported by 18 patients. None of these were classified

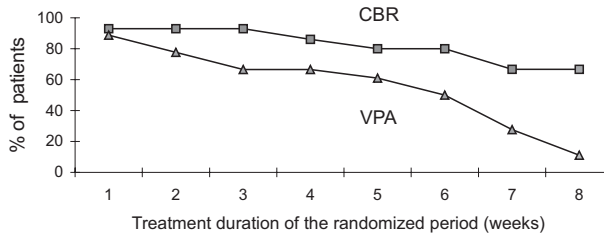

Fig. 2. Duration of exposure to medication with carbatrol (CBR) or valproate (VPA)

as serious (Tab. 4). There was no significant difference between the treatment regimes. Laboratory findings, vital signs and general physical examination did not show significant difference between the CBR and the VPA groups.

Mean plasma concentrations of the CBZ are summarized in Table 5. There was no significant difference between the baseline CBZ concentrations after 4 weeks of the treatment with CBZ. Mean plasma baseline CBZ concentration was 7.28 ± 0.44 μg/ml, and after run-in period the mean plasma levels of CBR were slightly higher 7.43 ± 0.51 μg/ml.

DISCUSSION

The present study has shown that CBR at doses 800, 1200 and 1600 mg was more efficacious compared to VPA in epileptic patients with refractory partial complex seizures. The dose of 15 mg/kg/day of VPA was chosen as that one recommended during the initial period of the therapy. It appeared that this dose could be insufficient in cases of refractory epilepsy because 17 patients were given supplementary PHT and another 3 PB at therapeutic doses. In patients with partial complex seizures, CBR reduced significantly the seizure frequency compared with patients who were given VPA. The intergroup difference has substantiated antiepileptic efficacy of CBR. In general, during a 3-month therapy CBR was well tolerated. The most frequent complaints included headache, dizzines, somnolence and memory impairment, however, due to too small group of patients statistical significance could not be calculated. None of the patients treated either with VPA or CBR was excluded from the study due to adverse effects of the drugs. No significant difference was found between the baseline blood plasma CBZ concentration and that one following the 4 week therapy with CBR.

The results of the trial have demonstrated clear antiepileptic efficacy of CBR in cases of partial complex seizures. CBZ formulations are drug of choice in the therapy of epilepsy. Due to introducing new formulations of CBZ (retard forms, slow release or oxcarbazepine) the drug is still "new" [14]. CBZ is used in the treatment of psychiatric disorders, nocturnal enuresis and migraine [1, 10, 16, 18, 20].

The new structure of CBR tablet is modern and may improve the pharmacological profile of this drug. Registration of CBR in the US, and results our investigations too, open a new perspective of improving control of epileptic seizures.

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