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Effect of levetiracetam in patients with epilepsy and interictal epileptiform discharges

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The effect of acute treatment with the new antiepileptic drug (AED) levetiracetam (Keppra®) on the frequency of interictal epileptiform discharges (IEDs) was evaluated in a double-blind, placebo-controlled, crossover study with therapeutic drug monitoring and serial electroencephalographic (EEG) observations. Acute (500 mg twice daily) and chronic (individualized, 500–1000 mg twice daily) doses of levetiracetam were administered as an add-on to current AED treatment. Efficacy was tested by measuring the frequency of IEDs in EEG recordings and the number of seizures. A single acute dose of levetiracetam induced a reduction of IEDs in eight out of ten patients. During the acute phase, an insufficient number of seizures occurred for analysis. During chronic treatment over 8 weeks, seven patients showed a reduction in seizure frequency (responder rate), and one patient remained seizure free. No correlation was seen between levetiracetam levels and IED frequency. Doses of levetiracetam of up to 2000 mg/day were well tolerated, and no interactions were seen with concomitant AEDs.

Key words: antiepileptic drugs; interictal epileptiform discharges; levetiracetam.

INTRODUCTION

Highly variable and unpredictable expression of the clinical manifestations of epilepsy often confounds assessment of the efficacy of antiepileptic drugs (AEDs) in short-term studies. In generalized epilepsy (at least in some syndromes), there is a strong correlation between seizures and spontaneous or provoked epileptiform spike-and-wave discharges in an electroencephalogram (EEG). Furthermore, these discharges have been used in the photosensitive model as a surrogate measure of potential drug efficacy [1,2].

For partial epilepsies, the relation between seizures and interictal epileptiform discharges (IEDs) is more controversial, but some interictal epileptiform activities have subtle clinical manifestations. It is important to know whether a new AED can have an effect on these IEDs, defined as a sharp transient, easily distinguishable from the background, having a duration of less than 70 milliseconds for a spike and 70–200 milliseconds for a sharp wave [3–5].

Monitoring IED frequency to measure antiepileptic activity is useful for the early assessment of potential AEDs, since the effect of acute doses can be studied. Suppression of IEDs is variably correlated with AED plasma levels, depending on the AED [6]. Diazepam, phenobarbital and phenytoin all show a correlation between suppression of IEDs and AED plasma concentration [7–9], while carbamazepine and valproate show a variable correlation [10,11].

Levetiracetam is a novel AED registered recently in 22 countries, including the United States, the European Union and Australia. Its efficacy in partial seizures, broad-spectrum potential, good tolerability, and nearly ideal pharmacokinetic profile make levetiracetam a promising new agent [12].

Studies in animal epilepsy models have demonstrated antiepileptic and potential antiepileptogenic action of levetiracetam. Unlike conventional AEDs, levetiracetam is inactive in classical screening models for acute seizures, such as maximal electroconvulsive shock and pentylenetetrazol seizure tests, but provides

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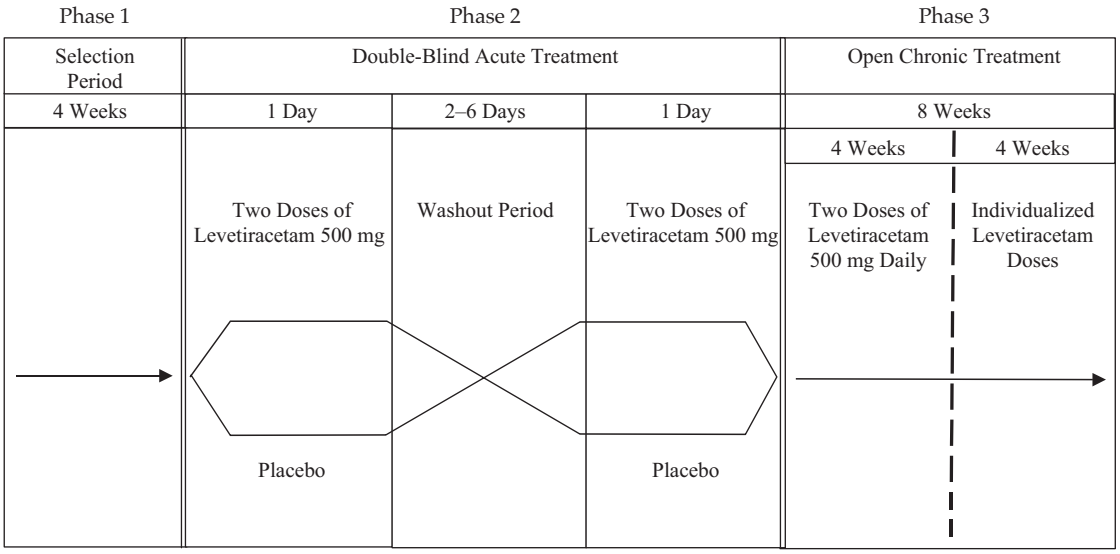

Fig. 1: Study design.

potent protection against seizures in animal models of partial and generalized epilepsy [13]. In patients with photosensitive epilepsy, levetiracetam has been shown to diminish or abolish sensitivity to photic stimuli. Following a single dose of levetiracetam, patients exhibited a long-lasting (up to 30 hours), initial dose-dependent reduction in photosensitivity [14].

The objective of this study was to determine the efficacy of acute levetiracetam treatment on IEDs in patients with partial epilepsy and evaluate the clinical effect of chronic treatment with individualized doses.

METHODS

Patient selection

Ten (six female and four male) epilepsy patients with partial seizures were included in this single-center study. The primary criterion for patient selection was expression of frequent IEDs in EEG recordings. Subjects in this study were taking a stable regimen of at most two concomitant AEDs, such as carbamazepine, clobazam, phenytoin, primidone, valproate sodium, and valproic acid.

Study design

This study was conducted in three phases (Fig. 1).

In the first phase, potential subjects were evaluated for four weeks to acquire baseline data and determine appropriateness for inclusion. Seizure count and IED frequency in EEG were monitored, a general medical history was taken, and subjects received a physical examination, an electrocardiogram (ECG), blood screen and urine analysis.

In the second phase, the acute treatment phase, eligible patients received a single-day supply of levetiracetam, 500 mg twice daily, or placebo in a double-blind crossover design. In the first part of the acute phase, five patients received levetiracetam and five received placebo. EEGs were recorded with a 32-channel amplifier using collodium-fixed gold cup-electrodes under standardized vigilance conditions. One standard 20 minutes duration EEG consisted of recordings under four different conditions: 5 minutes in a relaxed state with eyes closed, 5 minutes of mental activity, 5 minutes of forced hyperventilation and 5 minutes post-hyperventilation. Six EEG recordings were taken at a rate of one every 3 hours following dose administration. Blood samples to assess plasma AED levels were also taken every 3 hours following dose administration. EEGs were continuously sampled by a data-processing computer and stored on an optical disk. Spikes in the EEG were detected and counted with an automatic spike-detection program (MONITOR, Version 5.0, Stellate System, Montreal) and visually edited by a blind reader.

After 2 to 6 days without study drug, the two patient populations were switched so that the placebo group now received levetiracetam and the previous levetiracetam group received placebo. Again, each patient underwent six EEG recordings and blood samples were taken every 3 hours following drug administration. A full blood screen and urinalysis were conducted at the end of the acute phase.

The third phase consisted of 8 weeks of levetiracetam chronic treatment. For the first 4 weeks, levetiracetam was administered at a dosage of 500 mg

twice daily. During the second 4-week period, the levetiracetam dosage was adjusted up or down for each individual, depending on the outcome of the first 4-week session. Full blood screen and urinalysis were conducted at the end of each 4-week session. At the end of the chronic treatment phase, patients were allowed to continue with levetiracetam treatment or to gradually withdraw.

Assessment

The primary efficacy variable measured was the percentage difference in the number of IEDs between levetiracetam treatment (six EEGs) and placebo treatment (six EEGs) during the acute treatment phase. EEGs were therefore recorded at different times after the dose intake and were analysed together for specific conditions and for the whole. Secondary efficacy variables included number of seizures and pharmacokinetic data (levetiracetam and AED plasma levels). For assessing tolerability and safety, adverse events were recorded and blood and urine were collected at the end of every testing day during the acute period and every 4 weeks during the chronic treatment period. ECGs were performed at baseline, during the acute treatment period and at the end of the study.

Statistical analysis

The comparison of the effects of levetiracetam against placebo during the acute treatment phase was carried out on the basis of the primary efficacy criterion. To take into account the repeated measurements of IEDs at non-constant time interval, the AUC of the number of IEDs (the total of all test conditions, was computed using the linear trapezoidal rule and analysed by the two-period crossover analysis method[15]. The relation between the number of IEDs and levetiracetam plasma concentration at the same time point was examined for the first EEG period (relaxed conditions) using descriptive correlation methods. For the whole treatment phase, the daily number of seizures was calculated for each patient.

RESULTS

Demographic data

The demographic characteristics are shown in Table 1. The average age of the 10 patients was 25 years (range, 16 to 35 years). The age of first seizure ranged from 6 weeks to 14 years. The etiology of epilepsy was cryptogenic in five patients, and symptomatic in the remaining patients (two postencephalitis, two postperinatal brain damage, and one posttraumatic).

EEG

The percentage difference in AUC of IEDs between levetiracetam treatment and placebo is summarized in Table 2 for the different conditions and for the entire EEGs, data from the six recordings being pooled together. In eight of the ten patients, there was a consistent and major decrease in the AUC of IEDs following acute levetiracetam treatment. While percentage differences in AUC of IEDs were observed under all conditions, in most patients the difference was more obvious during the awake stage. No correlation was found between the AUC of IEDs and the AUC of levetiracetam plasma levels.

Chronic treatment: seizure count

During the 8 weeks of chronic levetiracetam treatment, the number of seizures per day in most patients was low. However, five patients showed a decrease (50% responder rate) in the number of seizures per day with chronic treatment compared with baseline response. One patient remained seizure free throughout levetiracetam treatment, while this patient had had seven seizures per month prior to treatment.

Safety

Acute treatment period

Levetiracetam was generally well tolerated with a dose of 1000 mg during acute treatment. A total of six adverse events were reported in four patients. Only one of the adverse events, mild dizziness, was reported by a patient following treatment with levetiracetam. All other adverse events, including abdominal pain and menstrual disorder, vomiting and urinary tract infection, and nausea and vomiting, occurred during the placebo period or after the placebo washout period. With the exception of vomiting (moderate), all adverse events were mild and considered possibly related to treatment. There were no relevant changes in concomitant AED plasma levels attributable to levetiracetam.

Chronic treatment period

Levetiracetam was generally well-tolerated using up to a maximum dose of 3000 mg/day. During 8 weeks of treatment, 31 adverse events were reported. One was severe (pain in the left ear), and none was clearly

Table 1: Demographics.

Treatment number and sequence	Gender	Age (years)	Age at onset of epilepsy (years)	Etiology	Number of seizures during last month	Concomitant treatment
LEV → PLC						
01	F	25	9	Unknown	6	PHT-VPA
03	F	25	11	Unknown	6	PHT
06	F	21	10	Unknown	12	PHT-CLB
08	M	24	1.5	Encephalitis	7	CBZ-VPA
10	F	18	10	Unknown	360	PHT-PRM
PLC → LEV						
02	F	32	14	Unknown	5	CBZ-CLB
04	M	16	3.5	Encephalitis	6	CBZ-VPA
05	M	31	7	Head injury	4	PHT-CLB
07	F	23	6 weeks	Perinatal asphyxia	150	NONE
09	M	35	6	Perinatal asphyxia	17	PHT

CBZ = carbamazepine; CLB = clobazam; LEV = levetiracetam; PHT = phenytoin; PLC = placebo; PRM = primidone; VPA = valproic acid.

Table 2: Percentage difference in AUC of IEDs between levetiracetam and placebo (expressed in % of placebo) following acute treatment under various test conditions.

Patient	Awake	Counting	Hyperventilation	Post-hyperventilation	Total
45/01	NA	NA	NA	NA	−97%[a]
45/02	−62%	−52%	−53%	84%	−56%
45/03	−37%	−40%	−28%	42%	−36%
45/04	−70%	+6%	−14%	−23%	−30%
45/05	+143%	+30%	+58%	+82%	+72%
45/06	+174%	+75%	+85%	+325%	+119%
45/07	−72%	−68%	−72%	−74%	−71%
45/08	−64%	−65%	−77%	−79%	−71%
45/09	−76%	−78%	−70%	−72%	−72%
45/10	−92%	−90%	−74%	−93%	−83%

[a] For this patient, the number of discharges was not available for all conditions, thus only a 'mean', equal to the number of discharges divided by the number of conditions has been used.

related to treatment. There were no ECG changes nor significant changes in blood and urinalysis.

DISCUSSION AND CONCLUSIONS

In this Phase II study, levetiracetam reduced the number of IEDs in epilepsy patients with partial seizures and frequent IEDs. Eight out of 10 patients treated with levetiracetam experienced a decrease in IEDs compared with patients receiving placebo. These findings are consistent with studies of diazepam, phenobarbital, and phenytoin, which also show a decrease or a suppression of paroxysmal response on EEG[6]. IEDs in partial epilepsy are often more easily recorded from temporal lobe epilepsy and could be the EEG sign of an active electrogenesis[16]. On the other hand, IEDs in generalized epilepsies appear to be familial and to be related to some genetic trait[17,18] and could translate the EEG sign of hyperexcitability.

Seizures were not numerous enough to allow statistical analysis. However, seizures were less numerous in five patients treated with levetiracetam, suggesting clinical efficacy. Levetiracetam was well tolerated, and no patients dropped out because of adverse events related to levetiracetam.

No correlation was found between the percentage difference in AUC of IED frequency and levetiracetam plasma levels. This is in contrast to findings on suppression of the photoparoxysmal response, where the initial suppression was dose dependent and correlated with levetiracetam plasma levels. However, the effect persisted even after serum levels of levetiracetam were no longer recordable. A similar effect on generalized spike-and-wave discharges has been described in relation to valproic acid[19–21]. These findings with levetiracetam strengthen the view that the mechanisms for genetic photoparoxysmal spikes and interictal discharges related to cryptogenic/symptomatic epilepsies are different.

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