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Brief Reports

Levetiracetam in Patients With Cortical Myoclonus: A Clinical and Electrophysiological Study

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Abstract: **Levetiracetam is a new antiepileptic agent that exerts antimyoclonic effects. We conducted an open-label trial to evaluate the effect of levetiracetam in chronic cortical myoclonus of diverse etiologies and to determine whether levetiracetam affects electrophysiological findings. Sixteen patients, aged between 19 and 72 years, with refractory, chronic, cortical myoclonus were recruited. We assessed myoclonus severity with the Unified Myoclonus Rating Scale (UMRS). The electrophysiological study comprised jerk-locked averaging, somatosensory evoked potentials (SEPs), and long loop reflex I. Levetiracetam was administered add-on at a starting dose of 500 mg twice per day up to the target dose of 50 mg/kg/day. Patients were reevaluated clinically and electrophysiologically 2 weeks after the titration phase. Fourteen patients completed the trial. Posttreatment UMRS scores showed an improvement of myoclonus in all cases. Pretreatment, 9 patients had "giant" SEPs. Posttreatment, the amplitude of these SEPs was reduced by more than 50% in 3 of 9 patients, and the mean N20-P25 amplitude was reduced significantly. Pre- and posttreatment SEP amplitude was not related to myoclonus severity or duration. Levetiracetam is a promising and a relatively easy-to-test antimyoclonic agent, which has the potential to improve significantly the patient's disability; however, its long-term efficacy should be verified in larger controlled studies.** © 2005 Movement Disorder Society

Key words: cortical myoclonus; levetiracetam; electrophysiology; SEPs

Conflict of Interest Disclosure: This study was not supported by any specific funding or by any pharmaceutical company. Two randomized trials (N166 and N167 UCB studies) with levetiracetam in juvenile myoclonic epilepsy are ongoing at the Epilepsy Center of the University of Naples "Federico II."

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Chronic myoclonus is often associated with severe functional disability and is frequently intractable to currently used antiepileptic drugs.[1] Piracetam at high doses is effective mainly in cases of myoclonus of cortical origin.[2,3] Levetiracetam is a new antiepileptic agent, closely related to piracetam, and has a broad spectrum of activity including an antimyoclonic effect.[4–6]

We have conducted a short, open-label, add-on trial to evaluate the antimyoclonic effect and tolerability of orally administrated levetiracetam in patients with chronic cortical myoclonus of various degrees of severity and of different causes. We have also determined whether levetiracetam induced changes in the patients' electrophysiological findings.

PATIENTS AND METHODS

Definitions

Cortical myoclonus is defined as myoclonus due to hyperexcitability of the sensorimotor cortex in which each jerk results from a neuronal discharge in the sensorimotor cortex,[7] as demonstrated by means of an electrophysiological study. Chronic myoclonus is myoclonus without remission for at least 1 year, and refractory myoclonus is myoclonus partially responsive or unresponsive to at least two conventional antimyoclonic drugs (valproate, clonazepam, primidone, phenobarbital, and piracetam).

Patients affected by chronic, refractory cortical myoclonus entered the study. The study was conducted according to the Declaration of Helsinki criteria (1983). Each subject was informed adequately of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researchers, the anticipated benefits and potential risks of the study, and the discomfort that it might entail. After ensuring that the patient had understood the information provided, we obtained the patient's freely given written informed consent. Every precaution was taken to respect the privacy of the subject, and the confidentiality of the patient's information.

Patients

Sixteen patients (10 men, 6 women) aged between 19 and 72 years (mean age, 39.6 years), monitored at the Epilepsy Center of the University of Naples Federico II, entered the study. Their clinical data are reported in Table 1. Six patients had a diagnosis of Unverricht-Lundborg disease (EPM1) confirmed by a mutation in the cystatin B gene, two of Lafora disease (EPM2) confirmed by skin biopsy, and eight patients had benign adult familial myoclonic epilepsy (BAFME), according to the diagnostic criteria reported elsewhere.[8] The severity of myoclonus differed depending on the cause and duration of the disease. The duration of myoclonus ranged from 3 to 42 years (mean duration, 20.6 years). Four patients (two EPM1 and two EPM2) also showed negative myoclonus. All patients had previously experienced generalized tonic–clonic seizures controlled for several years in all except EPM2 patients. Patients were taking a mean of two other antiepileptic drugs at the beginning of the trial. Eight patients (4 EPM1, 3 BAFME, and 1 EPM2) had taken oral piracetam 6 to 24 g/day (mean: 11.25 days) for 6 to 16 weeks (mean duration, 12.25 weeks). Five patients benefited from this treatment and did not suffer any untoward effects, but its efficacy decreased from between 12 and 16 weeks of administration, and the drug was withdrawn.

We evaluated the severity of myoclonus from video-electroencephalograph (EEG) recordings made during performance of the Unified Myoclonus Rating Scale (UMRS) in each subject before levetiracetam add-on and 2 weeks after the end of the titration phase. The UMRS is a statistically validated clinical rating instrument for myoclonus.[1,4] Each video-EEG was viewed independently and the patient's UMRS score was determined by two authors blinded to the patient's therapy. Before and after the trial, patients underwent physical examination, urinalysis, complete blood cell count, liver function tests, and electrolyte analysis.

Electrophysiological Evaluation

All patients underwent EEG-polygraphy and jerk-locked averaging. Right median nerve somatosensory evoked potentials (SEPs) and long loop reflex I were evaluated in 14 patients. Cortical myoclonus (including negative myoclonus) was diagnosed from electrophysiological evidence of cortical reflex myoclonus.[9] SEPs were judged "giant" if N20-P25 and P25-N35 exceeded 8.6 mV and 8.4 mV, respectively.[9] The electrophysiological study was repeated 2 weeks after completion of the titration phase.

Treatment Design

Levetiracetam was orally administered at a starting dose of 500 mg twice daily for 1 week followed by increments of 500 mg twice daily each week up to the target dose of 50 mg/kg/day. The titration phase included the week in which the target dose was reached. The drug was discontinued in case of intolerable side effects. The dosage of concomitant antiepileptic drugs remained constant for at least three months before the beginning to the

TABLE 1. *Clinical data of the 16 patients with chronic cortical myoclonus*

Patient/gender/ age (yr)	Diagnosis	Disease duration (yr)	Co-medications (mg/day)	Levetiracetam	
				Dose (mg/day)	Duration* (wk)
1/M/42	EPM1	28	VPA (1,500)	3,000	5
2/M/39	EPM1	24	VPA (1,000)	3,000	5
3/M/46	EPM1	32	VPA (1,500) CNZ (2,4)	3,000	5
4/M/42	EPM1	28	VPA (1,500) CNZ (2) PB (100) ACZ (250)	3,000	5
5/F/43	EPM1	29	VPA (1,500) CNZ (2,4)	3,000	5
6/M/32	EPM1	23	VPA (500) ACZ (250) PB (100)	4,000	6
7/F/19	EPM2	3	VPA (1,200) CNZ (2,4) LTG (100)	4,000	6
8/F/20	EPM2	3	VPA (1,200) CNZ (4) LTG (100)	4,000	6
9/M/38	BAFME	13	VPA (1,000)CNZ (2,4)	3,000	5
10/M/43	BAFME	15	VPA (1,000)	3,000	5
11/M/46	BAFME	20	VPA (500) PB (100)	3,000	5
12/M/39	BAFME	26	VPA (500) PB (100)	3,000	5
13/F/72	BAFME	42	PB (100)	3,000	5
14/F/41	BAFME	18	VPA (500)	3,000	5
15/M/38	BAFME	17	CBZ (200) PB (150)	1,000	Drop out
16/F/34	BAFME	9	VPA (500)CNZ (0,5)	1,000	Drop out

*Including 3–4 weeks of the titration phase.

EPM1, Unverricht-Lundborg disease; VPA, valproate; CNZ, clonazepam; PB, phenobarbital; ACZ, acetazolamide; LTG, lamotrigine; EPM2, Lafora disease; BAFME, benign familial myoclonic epilepsy.

end of the trial. Plasma levels of antiepileptic drugs were monitored monthly. Piracetam was stopped at least 6 months before the onset of the levetiracetam trial.

Statistical Analysis

We used the Wilcoxon matched-pairs test to compare mean pre- and posttreatment scores for each UMRS section and changes in SEP findings.

RESULTS

Clinical Evaluation

During the titration phase, 2 patients withdrew from the study because of sedation and fatigue and were excluded from further analysis; 14 patients completed the trial. The levetiracetam dose reached was between 3,000 and 4,000 mg/day (mean dose, 3,214 mg/day; Table 1). In all patients, add-on levetiracetam was associated with clinical improvement of myoclonus and a significant lowering of the mean scores of all UMRS sections except the negative myoclonus sections (Fig. 1). The effect of levetiracetam was not related to disease duration and cause or to the severity of myoclonus. The frequency of generalized tonic-clonic seizures was reduced in EPM2 patients but, given the low sample size, a statistical evaluation of global seizure rate was not possible. Levetiracetam was well tolerated by subjects who completed the study, and there were no changes in the plasma level of concomitant antiepileptic drugs during treatment.

Electrophysiological Study

Apart from a reduction of myoclonus, there were no significant changes at the follow-up EEG or polygraphic examinations. Treatment did not affect photosensitivity. Before levetiracetam treatment, 9 of 14 cases who completed the study showed giant SEPs (Table 2). The amplitude of giant SEPs was reduced by more than 50% in 3 cases at the follow-up study; latency was not affected by therapy. However, the mean N20-P25 amplitudes decreased significantly ($P < 0.01$) from 14.7 ± 13.9 mV to 9.7 ± 7.3 mV. There was no significant difference between the pre- and posttreatment P25-N30 amplitudes (27.6 ± 33.1 vs. 17.7 ± 13.3 mV). The amplitude of SEPs was not related to the severity or duration of myoclonus. Similarly, there was no significant difference in pre- and posttreatment long loop reflex I. After completion of the trial, all patients remained on levetiracetam

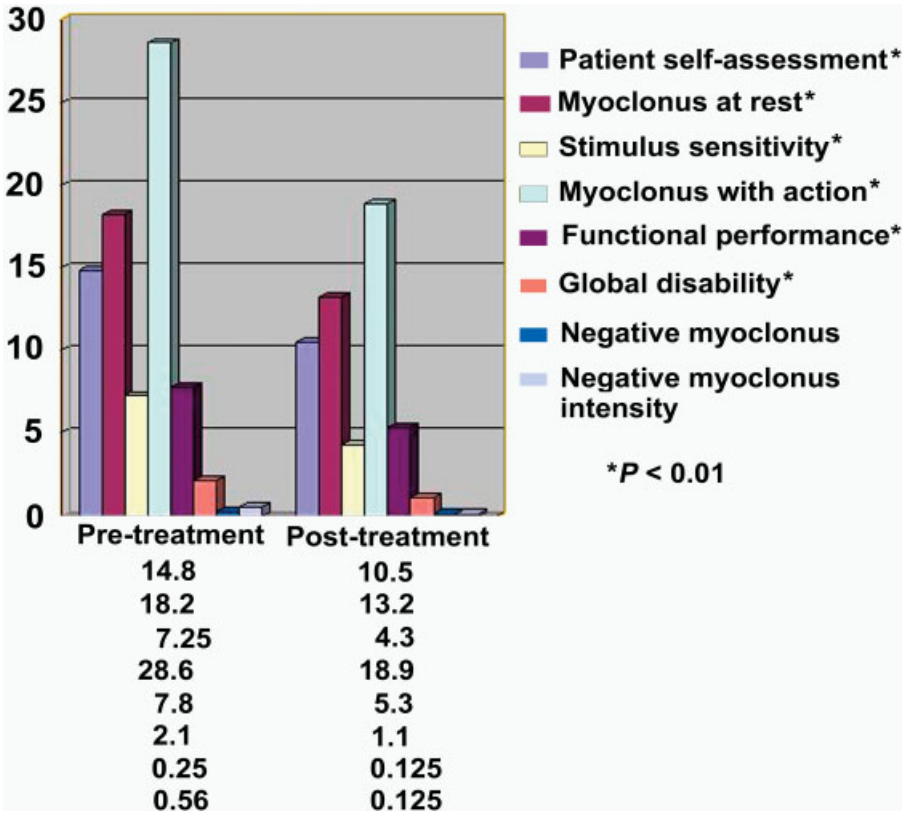

FIG. 1. Mean UMRS scores before and after the trial compared by using the Wilcoxon signed rank test. Levetiracetam treatment was associated with a significant reduction in all sections, except the negative myoclonus section. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 2. *Somatosensory evoked potential data of 14 patients with chronic cortical myoclonus at baseline and after levetiracetam treatment*

	Baseline amplitude (μV)		Follow-up amplitude (μV)	
Patient	N20-P25	P25-N30	N20-P25	P25-N30
1[a]	10	17.8	6	12.8
2[a]	10.9	14.4	10	14
3	2.4	NP	NP	NP
5[a]	18.8	27.5	12	26.3
7[a]	51.4	130	20	31
8	5	6	4	3.9
9	2.4	4.3	NP	NP
10[a]	9	14.7	2	4
11[a]	10.6	20.6	6	18.8
12[a]	20	47.5	9	14
13[a]	37.5	38.4	26.6	49
14	7	10	6	13.8
15[a]	14	14.4	NP	NP
16	7	14	6	8
Mean (SD)	14.7 (13.9)*	27.6 (33.1)	9.7 (7.3)*	17.7 (13.3)

*$P < 0.01$.

[a]Patients with both giant somatosensory evoked potential (SEP) components at baseline.

NP, not performed; SD, standard deviation.

therapy. To date, treatment duration ranges between 9 to over 11 months.

DISCUSSION

Chronic myoclonus may occur in various neurological disorders. It is often associated with severe disability and is difficult to treat. Conventional antiepileptic drugs such as valproate, clonazepam, primidone, and phenobarbital may be poorly effective in monotherapy and even in combination.[2] Piracetam is an effective antimyoclonic agent, but the exceedingly high doses needed to reach efficacy can impede compliance.[5]

Levetiracetam is a new antiepileptic agent that is effective in partial and generalized epilepsies. The recent finding that the synaptic vesicle protein SV2A is the binding site of levetiracetam in the brain shows that it acts differently from other antiepileptic drugs.[10] In addition, a subtype of N-type channel sensitive to levetiracetam has been implicated in the drug's antiepileptic effect.[11] Levetiracetam could also exert its effect by activating potassium channels and through zinc-mediation of GABA responses[5]; however, the molecular basis of the antiepileptic effect of levetiracetam has yet to be elucidated.

A body of evidence suggests that levetiracetam may be effective in both positive and negative myoclonus,[4–6,12] and in patients with posthypoxic and postencephalitic myoclonus.[13] In a previous open-label trial conducted in 8 patients with chronic myoclonus, levetiracetam (2,000 mg/day) reduced the myoclonus as evaluated with the UMRS, although a significant difference was found only as regards the patients' self-assessment and the physician's assessment of disability.[4] Crest and colleagues[5] found that levetiracetam reduced myoclonus in 5 of 9 patients with progressive myoclonic epilepsy. Finally, in another open-label trial, levetiracetam exerted an antimyoclonic effect in 8 of 13 EPM1 patients and was well tolerated.[6]

In our trial, levetiracetam administered at the dose of 3,000 to 4,000 mg/day resulted in a significant improvement of myoclonus. Except for two sections, all mean posttreatment UMRS scores were significantly lower than were pretreatment scores. The more substantial improvement with respect to that reported by Frucht and colleagues[4] may be due to the higher dose of the drug (2,000 vs. 3,000–4,000 mg/day) used in our study. It is noteworthy that levetiracetam was associated to significant improvement of myoclonus also in patients with low baseline UMRS scores. The effect was not related to disease duration or to the severity and cause of myoclonus. Although generalized tonic-clonic seizures were reduced in the two EPM2 patients, the efficacy of levetiracetam against major seizures cannot be assessed in this study. Levetiracetam was generally well tolerated and only 2 patients withdrew during the titration phase due to sedation and fatigue. In these patients, the abrupt self-withdrawal from treatment did not cause any problems and patients returned to their baseline condition with no exacerbation of myoclonus.

In a previous long-term follow-up, levetiracetam's antimyoclonic effectiveness decreased with time.[5] This may be linked to the natural course of the underlying disease or to a loss of effectiveness of the drug. Given the relatively short follow-up period in our study, we are unable to comment on attenuation of efficacy with time.

Ours is the first study conducted with levetiracetam in BAFME patients. This is an autosomal dominant-inherited syndrome associating cortical tremor, myoclonus and seizures. Previously, BAFME was generally treated with valproate and clonazepam.[8] Our data show that these patient may also benefit from the good antimyoclonic effect of levetiracetam.

We found that levetiracetam was associated with a decreased amplitude of cortical SEPs in some patients. In addition, piracetam has been reported to reduce the amplitude of P25 of median nerve SEPs in patients with cortical myoclonus.[2,14] To our knowledge, however, our trial is the first to show that levetiracetam may positively affect the cortical components of SEPs. Of our 14 patients, 9 showed giant SEPs at the basal evaluation, irrespective of the severity, etiology, and duration of the

myoclonus disease, as well as of the concomitant antiepileptic therapy or their plasma levels. Posttreatment, the amplitude of giant SEPs was reduced by more than 50% in 3 of 9 patients. The mean N20-P25 amplitude also was reduced significantly (Table 2). The results of the electrophysiological study coincide with the mean clinical improvement in our patients as evaluated by the UMRS. In most patients, however, giant SEPs did not necessarily become smaller even when the drug was associated with significant improvement of myoclonus. This suggests that levetiracetam's antimyoclonic effect is not necessarily mediated through the mechanisms by which SEPs are enhanced. It is worth evaluating further whether SEPs might be a tool with which to compare patients before and after levetiracetam treatment.

Being an uncontrolled, short-term trial, our results about levetiracetam efficacy should be regarded preliminary and be interpreted with caution. Chronic myoclonus, which impinges on all aspects of the patient's daily life, can be refractory to various antiepileptic drugs. Levetiracetam is a promising and a relatively easy-to-test antimyoclonic agent that has the potential to improve significantly the patient's disability. Its long-term efficacy, however, should be verified in larger controlled studies.

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Parkinson's Disease Mortality Among Male Anesthesiologists and Internists

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Abstract: **Clusters of Parkinson's disease (PD) among healthcare professionals have been interpreted as evidence of an infectious etiology. Anesthetic gases have also been associated with parkinsonism symptoms and PD among patients undergoing general anesthesia. We investigated PD mortality among large cohorts of male U.S. anesthesiologists (n = 33,040) and internal medicine physicians (n = 33,044). PD mortality for any mention on a death certificate was lower than rates in U.S. men during 1979–1995 for both groups, although anesthesiologists had a significantly elevated risk for PD as underlying cause of death for 10-year follow-up. Direct comparisons of mortality between the two cohorts indicated excess PD mortality in anesthesi-**

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