An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy

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ABSTRACT Objective: To conduct an open-label, add-on trial on safety and efficacy of levetiracetam in severe myoclonic epilepsy of infancy (SMEI). **Patients and Methods:** SMEI patients were recruited from different centers according to the following criteria: age ≥3 years; at least four tonic-clonic seizures/month during the last 8 weeks; previous use of at least two drugs. Levetiracetam was orally administrated at starting dose of approximately 10 mg/kg/day up to 50 to 60 mg/kg/day in two doses. Treatment period included a 5- to 6-week up-titration phase and a 12-week evaluation phase. Efficacy variables were responder rate by seizure type and reduction of the mean number per week of each seizure type. Analysis was performed using Fisher exact and Wilcoxon tests. **Results:** Twenty-eight patients (mean age: 9.4 ± 5.6 years) entered the study. Sixteen (57.1%) showed *SCN1A* mutations. Mean number of concomitant drugs was 2.5. Mean levetiracetam dose achieved was 2,016 mg/day. Twenty-three (82.1%) completed the trial. Responders were 64.2% for tonic-clonic, 60% for myoclonic, 60% for focal, and 44.4% for absence seizures. Number per week of tonic-clonic (median: 3 vs 1; $p = 0.0001$), myoclonic (median: 21 vs 3; $p = 0.002$), and focal seizures (median: 7.5 vs 3; $p = 0.031$) was significantly decreased compared to baseline. Levetiracetam effect was not related to age at onset and duration of epilepsy, genetic status, and concomitant therapy. Levetiracetam was well tolerated by subjects who completed the study. To date, follow-up ranges 6 to 36 months (mean, 16.2 ± 13.4). **Conclusion:** Levetiracetam add-on is effective and well tolerated in severe myoclonic epilepsy of infancy. Placebo-controlled studies should confirm these findings. **NEUROLOGY 2007;69:250–254**

Severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome is a drug-resistant epilepsy occurring in the first year of life of previously healthy children. The main clinical features are prolonged and repeated febrile and afebrile generalized or unilateral convulsive seizures. Between ages 1 and 4, other seizure types appear, including myoclonic and partial seizures.[1-3] EEG may show generalized as well as focal abnormalities and often photosensitivity at early stage. Psychomotor development is initially normal but stagnation begins around the second year of life.[1,3] Point mutations or deletions involving the voltage-gated sodium channel alpha-subunit gene (*SCN1A*) have been reported in a proportion of patients.[3-5]

Pharmacologic treatment of SMEI is disappointing. A combination of old (valproate, benzodiazepines) and new (topiramate, stiripentol) antiepileptic drugs (AEDs) is the mainstay of therapy.[2,3]

Levetiracetam is an AED with a unique preclinical profile and a mechanism of action distinct from that of other anticonvulsants. Recently, the synaptic vesicle protein SV2A was found to be the main levetiracetam binding site in the brain.[6]

Levetiracetam has been recently licensed for treatment of children with partial epilepsy and of drug-resistant myoclonic seizures in juvenile myoclonic epilepsy with good pharmacokinetic and tolerability profile.[7,8]

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Supported by the Italian League against Epilepsy and the Italian Ministry of Health (no. 132/03 to F.Z.).

Disclosure: The authors report no conflicts of interest.

Figure 1 Trial design

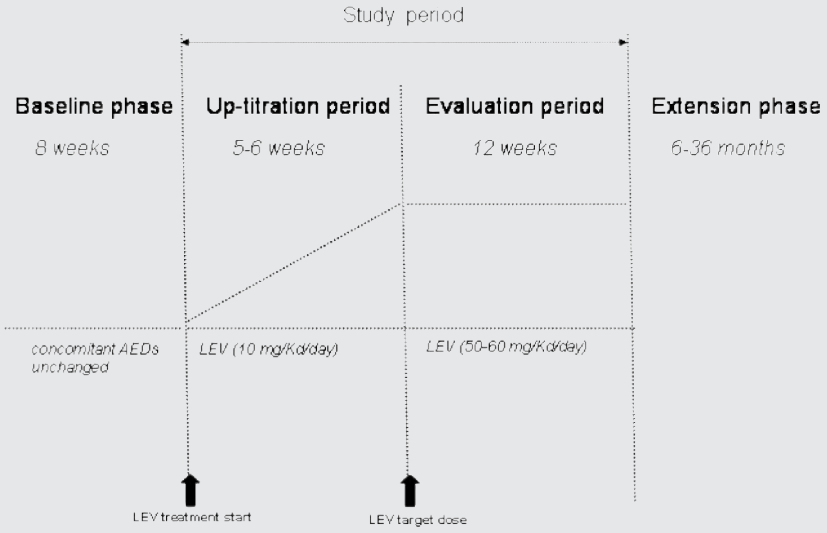


Table 1 Demographic and baseline characteristics of enrolled patients

Variable	Value
No. of patients (M/F)	28 (16/12)
Age, range (mean ± SD), y	3–23 (9.4 ± 5.6)
Epilepsy onset, range (mean ± SD), mo	2–15 (6.3 ± 3.1)
% *SCN1A* mutations	57.1
No. previous AEDs, range (mean)	3–7 (3.6)
No. concomitant AEDs, range (mean)	1–3 (2.5)

AEDs = antiepileptic drugs.

We conducted an open-label, add-on trial to evaluate the efficacy and safety of orally administrated levetiracetam in SMEI.

METHODS Patient population. Patients were recruited in an add-on, open-label study from seven different Italian Epilepsy Centres with the following inclusion criteria: age 3 years or older; diagnosis of SMEI, defined as early-onset febrile or afebrile seizures including tonic-clonic, myoclonic, absence, focal seizure types, generalized or focal EEG abnormalities, and initial normal psychomotor development followed by mental delay from the second year of life[1,3]; at least four tonic-clonic seizures a month during the last 8 weeks; previous use of at least two conventional AEDs; parents or caregivers able to comply regularly to drug therapy and seizure diary; and mutational testing of *SCN1A* accomplished.

Concomitant occurrence of acute medical illness or previous exposure to levetiracetam were exclusion criteria. The study was conducted according to the Declaration of Helsinki criteria and no pharmaceutical support was obtained. Approval from the Institutional Ethic Committees and informed consent signed by the parents was required. Family and personal history was taken and neurologic examinations performed in all patients. Epileptic seizures were classified according to the ILAE criteria.[9] *SCN1A* point mutations were tested by denaturing high performance liquid chromatography and direct sequencing; genomic deletions by fluorescence in situ hybridization.[4,5] IQ was evaluated by using the Brunet-Lezine (or Griffiths scales test) and Wechsler Intelligence Scale for Children–Revised, according to the patient's age.

Study design. Figure 1 shows the study design. This was an add-on, open-label trial consisting of an 8-week baseline period. Concomitant medications remained at unchanged doses for at least 2 months prior to study entry and throughout the duration of the study. Levetiracetam was administrated at starting dose of approximately 10 mg/kg/day followed by 10 mg/kg/day increments at 1-week intervals up to the dose of 50 to 60 mg/kg/day given in two divided doses. Titration phase included the week in which target dose was reached. The treatment period was composed of a 5- to 6-week up-titration phase and a 12-week evaluation phase. The use of benzodiazepines was generally avoided during the trial. However, parents and caregivers were allowed to administer oral or rectal benzodiazepines in case of long-lasting major epileptic seizures or status epilepticus.

Safety procedures. Adverse events were recorded on diary and levetiracetam discontinuation was undertaken in case of intolerable side effects or seizure aggravation. Moreover, neurologic examinations together with complete peripheral blood count, urinary analysis, and measurement of blood creatinine, alanine, and aminotransferase levels were performed at the end of the titration phase and at the end of the trial.

Clinical evaluation. Seizure type and frequency were recorded in an epilepsy diary by parents and caregivers both at home and at school over an 8-week period before starting levetiracetam treatment. Tonic-clonic, myoclonic, focal, and absence seizures were distinguished. Efficacy variables were responder rate by seizure type and reduction of the mean number per week of each seizure type. Responders were differentiated for category (>50% and >75% seizure reduction, and seizure-free). Patients experiencing ≤50% seizure reduction were considered as nonresponders. Efficacy variables were analyzed at the end of the evaluation period compared to the baseline. In addition, prolonged video-EEG recordings, including intermittent photic stimulation, were performed before, during (at the beginning of the evaluation period), and at the end of the trial.

After the end of the trial, patients entered an observational, extension study (figure 1).

Statistical analysis. Statistical analysis was performed using Fisher exact and Wilcoxon tests with MedCalc software.

RESULTS Patient population. Twenty-eight patients (16 M, 12 F), aged 3 to 23 years (mean, 9.4 ± 5.6), entered the study. Baseline demographic and seizure characteristics are summarized in table 1. Mean age at epilepsy onset was 6.3 ± 3.1 months (range: 2 to 15). Twenty-two patients experienced febrile seizures as first disease manifestation whereas initial manifestation was afebrile tonic or clonic or tonic-clonic in the remaining six. Mental retardation was moderate in 13, mild in 7, and severe in 8 subjects. Sixteen (57.1%) patients showed *SCN1A* mutations (9 missense, 5 truncating, 1 splice-site, 1 intragenic deletion). All patients were refractory, having been

Table 2 AEDs concomitant to levetiracetam therapy

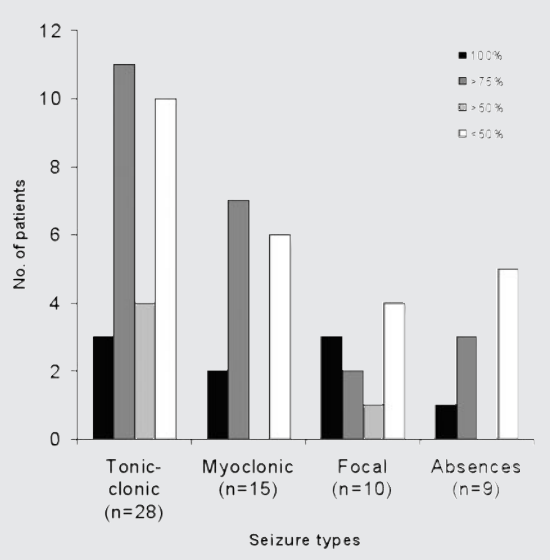
AEDs	No.	%
Valproate	23	82.1
Topiramate	13	46.4
Phenobarbital	6	25.0
Clobazam	5	20.8
Clonazepam	5	20.8
Stiripentol	4	16.6
Nitrazepam	1	4.1
Primidone	1	4.1

AEDs = antiepileptic drugs.

treated with a mean of 3.6 AEDs[3-7] before levetiracetam trial. Two patients had been previously treated with ketogenic diet. Concomitant AEDs during the study ranged from 1 to 3 (mean: 2.5) as shown in table 2.

Twenty-three out of 28 patients had more than one seizure type during the baseline period: 15 had two types, 6 had three types, and 2 had four seizure types. All children had tonic-clonic seizures during the baseline period whereas myoclonic seizures were observed in 15, focal seizures in 10, and absences in 9 patients. The median number of episodes per week was 3 ± 5.3 for tonic-clonic seizures, 14 ± 96.2 for myoclonic seizures, 14 ± 110.5 for absences, and 10 ± 14.5 for focal seizures. Three subjects had monthly episodes of status epilepticus generally needing benzodiazepines acute treatment during the baseline period. EEG recordings before the trial showed generalized spike-waves in 8 patients, focal or multifocal abnormalities in 7, both focal or generalized in 13. Two subjects showed photoparoxysmal response at the time of the trial.

Figure 2 Response to levetiracetam by seizure type



Response to levetiracetam by seizure type at the end of the trial compared to the baseline period.

Table 3 Effect on seizure frequency after levetiracetam treatment

Levetiracetam treatment	Number of seizures per week (median)		
	Tonic-clonic	Myoclonic	Focal
Before	3	21	7.5
After	1	3	3
p Value*	0.0001	0.002	0.031

*Wilcoxon test.

Efficacy. Twenty-three (82.1%) patients completed the trial. Mean levetiracetam dose achieved was 2,016 mg/day (range: 750 to 3,000). During the titration phase, 5 (17.8%) children withdrew, because of irritability (n = 2), cutaneous rash (1), worsening of myoclonic seizures (1), or thrombocytopenia (1).

Responders were 18/28 for tonic-clonic seizures (64.2%; 3 patients seizure free, 11 patients ≥75% seizure reduction, 4 patients >50% seizure reduction), 9/15 for myoclonic seizures (60%; 2 patients seizure free, 7 patients ≥75% seizure reduction), 6/10 for focal seizures (60%; 3 patients seizure free, 2 patients ≥75% seizure reduction, 1 patient >50% seizure reduction), and 4/9 for absences (44.4%; 1 patient seizure free, 3 patients ≥75% seizure reduction) (figure 2). Overall, 18 out of 28 patients were responders for at least one seizure type and 11/28 were responders for at least two seizure types.

Furthermore, number per week of tonic-clonic (median: 3 vs 1; $p = 0.0001$), myoclonic (median: 21 vs 3; $p = 0.002$), and focal seizures (median: 7.5 vs 3; $p = 0.031$) was decreased compared to baseline period (table 3) whereas no difference was observed for absence seizures ($p = 0.125$).

Levetiracetam effect was not related to sex, age at onset and duration of epilepsy, or concomitant AEDs therapy. Moreover, response to levetiracetam treatment did not differ between patients showing *SCN1A* mutations and those without *SCN1A* mutations ($p = 1.00$). One of three children with status epilepticus did not repeat the event whereas the other two experienced occasional episodes of status epilepticus but did not need benzodiazepine rescue. Video-EEG recordings revealed disappearance or clear improvement of paroxysmal abnormalities in 13 patients who completed the trial whereas EEG remained substantially unchanged in the remaining 10. Levetiracetam treatment did not affect photoparoxysmal response in any case.

Tolerability. Levetiracetam was well tolerated by subjects who completed the study. Mild and transitory sleepiness or sedation occurred in two subjects. There were no significant changes in laboratory examinations at the end of the trial.

Follow-up duration. To date, all patients who completed the trial are still on levetiracetam (mean follow-up: 16.2 ± 13.4 months; range: 6 to 36).

DISCUSSION

SMEI is one of the most deleterious epilepsy syndromes during childhood. Treatment of SMEI remains challenging and is based on prevention and control of hyperthermia, the use of low-dose maintenance AEDs therapy, and intermittent rescue treatment with benzodiazepines.[2,3] AEDs are usually limited to the combination of two broad-spectrum AEDs such as valproate and topiramate.[2,3] An alternative is the combination of valproate and stiripentol but the latter is available only in a limited number of countries.[12] There are few trials of AEDs in patients with SMEI: two open-label studies showing efficacy of topiramate[10,11] and one placebo-controlled study assessing the efficacy and tolerability of stiripentol.[12] In addition, preliminary data suggest a possible benefit of bromide,[13] zonisamide,[14] immunoglobulin,[2,3] and ketogenic diet.[15]

This first trial of levetiracetam in SMEI demonstrated that it is effective and well tolerated at a target dose of 50 to 60 mg/kg/day when given as adjunctive therapy.

Notably, levetiracetam showed good efficacy on tonic-clonic seizures, the most severe and often life-threatening seizure type in SMEI.[2,12]

The present study was not aimed to explore the correlation between EEG improvement and treatment outcome. However, in contrast to that previously reported,[16] photoparoxysmal response was not modified by levetiracetam in either. Specific studies should be performed to evaluate the EEG changes induced by levetiracetam treatment.

As expected by the peculiar mechanism of action of levetiracetam, the efficacy was not significantly different between *SCN1A* mutant and non-mutant patients.

Levetiracetam was well tolerated in patients who completed the study, according to its good tolerability profile.[7,8] However, 5 out of 28 (18%) patients stopped the trial because of mild and transient side effects, predominantly occurring during the initial phase of treatment.

Limitations of this study include the open-label design and the relatively short follow-up.

Thus, the results of this open-label, short-term trial should be regarded as preliminary and interpreted with caution. Nevertheless, the significant reduction of seizures in approximately two thirds of our patients suggests that levetiracetam is a promising broad-spectrum and easy-to-test drug in such a severe epileptic condition. Larger randomized placebo-controlled studies should confirm these data.

ACKNOWLEDGMENT

The authors thank Dr. Bruno Ferrò for helpful comments.

Received January 2, 2007. Accepted in final form March 7, 2007.

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New AAN Guideline on Lyme Disease Treatment Published

The AAN published a new clinical guideline on Lyme disease in the July 3, 2007, issue of *Neurology*. The guideline provides evidence-based recommendations on the treatment of nervous system Lyme disease and post-Lyme syndrome. Lyme disease is a multisystem infectious disease caused by the tick-borne spirochete, *Borrelia burgdorferi*, which frequently affects the nervous system. While guidelines exist to assist in the diagnosis of nervous system Lyme disease and for treatment of Lyme disease in general, there continues to be considerable controversy and uncertainty about the best approach to treatment of neuroborreliosis. To learn more, read the guidelines at *www.aan.com/go/practice/guidelines*.

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Neurology 2007;69;250-254
DOI 10.1212/01.wnl.0000265222.24102.db