Seizure (2007) **16**, 345—350

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy

S. Grosso [a], D.M. Cordelli [a], E. Franzoni [b], G. Coppola [c], G. Capovilla [d], N. Zamponi [e], A. Verrotti [f], G. Morgese [a], P. Balestri [a,*]

[a] *Pediatrics Department, University of Siena, Italy*
[b] *Center of Pediatric Neurology, Bologna University, Italy*
[c] *Institute of Child and Adolescence Neuropsychiatry, Second University of Naples, Italy*
[d] *Child Neuropsychiatry Unit, "C. Poma" Hospital, Mantova, Italy*
[e] *Pediatric Neurology Department, Children's Hospital G. Salesi, Ancona, Italy*
[f] *Section of Pediatrics, Department of Medicine, University of Chieti, Italy*

Received 26 July 2006; received in revised form 19 September 2006; accepted 20 February 2007

KEYWORDS
Levetiracetam;
Antiepileptic drug;
Drug resistant epilepsy;
Children;
Epilepsy syndromes

Summary The aim of this multicentric, retrospective, and uncontrolled study was to evaluate the efficacy and safety of levetiracetam (LEV) in 81 children younger than 4 years with refractory epilepsy. At an average follow-up period of 9 months, LEV administration was found to be effective in 30% of patients (responders showing more than a 50% decrease in seizure frequency) of whom 10 (12%) became seizure free. This efficacy was observed for focal (46%) as well as for generalized seizures (42%). In addition, in a group of 48 patients, we compared the initial efficacy (evaluated at an average of 3 months of follow-up) and the retention at a mean of 12 months of LEV, with regard to loss of efficacy (defined as the return to the baseline seizure frequency). Twenty-two patients (46%) were initial responders. After a minimum of 12 months of follow-up, 9 of 48 patients (19%) maintained the improvement, 4 (8%) of whom remained seizure free. A loss of efficacy was observed in 13 of the initial responders (59%). Maintained LEV efficacy was noted in patients with focal epilepsy and West syndrome. LEV was well tolerated. Adverse events were seen in 18 (34%) patients. The main side effects were drowsiness and nervousness. Adverse events were either tolerable or resolved in time with dosage reduction or discontinuation of the drug.

We conclude that LEV is safe and effective for a wide range of epileptic seizures and epilepsy syndromes and, therefore, represents a valid therapeutic option in infants and young children affected by epilepsy.

* Corresponding author at: Department of Pediatrics, Obstetrics and Reproductive Medicine, University of Siena, Via M. Bracci, Le Scotte, 53100 Siena, Italy. Tel.: +39 057 7586 522; fax: +39 057 7586 143.
E-mail address: balestri@unisi.it (P. Balestri).

1059-1311/$ — see front matter
doi:10.1016/j.seizure.2007.02.004

Introduction

Levetiracetam (LEV) is one of the latest antiepileptic drug (AED) available on the market.[1,2] Mechanisms underlying its antiepileptic activity are partially understood. LEV partially inhibits N-type high-voltage-activated Ca^{2+} currents and reduces the Ca^{2+} release from intraneuronal stores.[3] LEV is also able to reverse the effects of negative allosteric modulators of γ-aminobutyric acid (GABA) and glycine-gated currents.[4] LEV has a favorable pharmacokinetic profile characterized by rapid and almost complete absorption after oral administration, linear pharmacokinetics, minimal protein binding, predominantly renal excretion, and no significant drug interactions.[2,5] In children the pharmacokinetics resulted to be similar to that observed in adults, even though clearance is approximately 30—40% higher.[5] Although double blind placebo-controlled clinical trials demonstrated the efficacy of LEV in both adults[6,7] and children,[8] safety and efficacy of LEV in infancy remain to be ascertained.

Here we report on a retrospective, multicenter study which has been conducted in order to acquire further information about efficacy and tolerability of LEV in a pediatric population under four years of age affected by several types of seizures and epilepsy syndromes.

Patients and methods

Data were obtained from records of patients treated with LEV for epilepsy from January 2003 to June 2005. Data for an open, multicentered, retrospective study of children treated with LEV were collected from six pediatric neurology departments in Italy. Patients were selected by the following criteria: (i) aged less than 4 years; (ii) exhibiting at least four seizures a month during the 3 months before LEV was administered. Patients with progressive neurological disorders were excluded from the study. Family and personal histories were taken and neurological examinations performed on all patients. Details of sex, age, anti-epilepsy drug (AED) usage before LEV therapy, concomitant therapy, and duration of treatments and of epilepsy were collected. All patients underwent brain magnetic resonance imaging (MRI). Biochemical analyses, chromosomal investigations, and screening for metabolic disorders were carried out in all patients. Seizure types and epilepsy syndromes were classified in accordance with the International League against Epilepsy (ILAE) classifications, and the recently proposed diagnostic scheme for patients with seizures and epilepsy.[9—11]

Patients

A total of 81 children (36 girls and 45 boys) aged less than 4 years were recruited. Neuromotor retardation was observed in 60 (74%) patients and it was considered to be severe in 27, moderate in 15, and mild in 18. Mean seizure frequency was 42 seizures per month (range 16—162). The mean age to the first seizure was nine months (range 1 month—3.5 years), and mean duration of the epileptic history was 17 months (range 3—41 months). Epilepsy was symptomatic in 41 (50%) patients, probably symptomatic in 32 (40%), and idiopathic in 8 (10%). Focal seizures were observed in 44 (54%) patients, and generalized seizures in 57 (70%). In 17 (21%) patients, partial seizures evolved to secondary generalization. Twenty-four (30%) patients exhibited more than one type of seizure. Informed consent for LEV administration was obtained from the parents. The mean number of AEDs tried before starting LEV treatment was four (range 1—10). The number of AEDs administered when LEV treatment was started ranged from one to three (average two). Drugs administered at the outset of LEV therapy included valproate (41%), phenobarbital (31%), carbamazepine (27%), vigabatrin (26%), topiramate (22%), clonazepam (20%), lamotrigine (9%), oxcarbazepine (7%), chlormethyldiazepam (6%), and ACTH (10%).

Levetiracetam was administered in two equal daily doses of 5—10 mg/kg. The dose was increased every week up to a maximum of 62 mg/kg per day. In the event of an adverse reaction, the titration phase was prolonged based on the clinical condition. During treatment complete peripheral blood counts, urinary analysis, determinations of blood creatinine level and alanine and aspartate aminotransferase levels were taken.

Response

In comparison with baseline seizure frequency and severity, the response to LEV treatment was classified as follows: complete cessation (100% seizure control); very good (decrease in seizure frequency by 50—99%); minimal (21—50% seizure reduction with minimal change in seizure severity); unmodified (less than 20% seizure reduction) or worsening (increase seizure frequency to >50%). Physicians openly reported adverse events related to the drug administration.

LEV retention at 12 months

In a group of 48 patients, the initial LEV efficacy, defined as the number of responsive patients at a

minimum period of 3 months follow-up (range 2—4 months), was compared with the retention at 12 months (range 12—14) of LEV, to examine the loss of efficacy. Retention at 12 months of LEV, a composite measure of efficacy and adverse events in clinical practice, was defined as the percentage of patients still taking LEV after a minimum period of 12 months of follow-up (range 12—45 months). Loss of efficacy was defined as the return to the baseline seizure frequency.

Results

The mean age of patients at the time of initial LEV treatment was 27 months (range 2—46 months). The mean duration of treatment was 9.2 months (range 3—42 months). Mean LEV daily dose was 41 mg/kg (range 25—62 mg/kg per day).

Efficacy

At their last visit, 37 (46%) patients out of 81 were still being treated with LEV, whereas LEV had been stopped in the remaining 44 (54%) patients. Twenty-four (30%) patients were considered to be responders because they showed a reduction in their seizure frequency by more than 50%. Specifically, 10 (12%) children became seizure free, 14 (17%) showed a seizure reduction of more than 50%, and 18 (22%) showed seizure reduction of 20—50%. In 24 (30%) patients seizure frequency remained unchanged and in a further 15 (18%) patients seizures increased more than 50% in comparison with the baseline. In 13 (16%) nonresponders LEV was maintained because either seizures were reduced in severity or there were positive psychotropic effects. Seizure reduction was seen over a wide range of seizure types (Fig. 1) and epilepsy syndromes (Table 1). LEV appeared to be effective in both focal (46% of responders) and generalized epilepsy (42% of responders). Efficacy was also observed in three (12%) patients presenting with an unclassifiable type of epilepsy syndrome. In eight (10%) patients, the good initial response was lost within 4 weeks with seizure frequency returning to a pretreatment level.

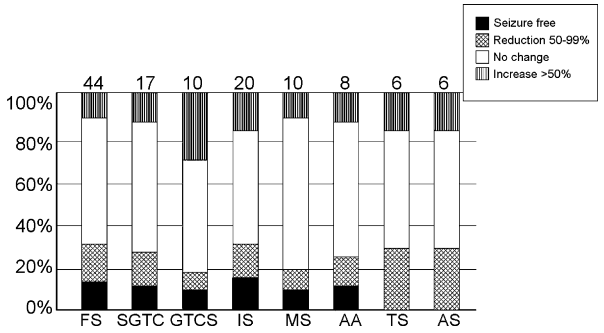

Figure 1 Efficacy of LEV on different seizure types (more than one type of seizures could be present in a single patient). FS: focal seizures; SGTC: secondary generalized tonic seizures; GTCS: generalized tonic—clonic seizures; IS: Infantile spasms; MS: myoclonic seizures; AA: atypical absences; TS: tonic seizures; AS: atonic seizures.

In two patients, one affected by focal epilepsy and one with West syndrome, LEV monotherapy was successful because both remained responders at the last follow-up visit. In a further six (7%) children, one or more concomitant drugs was reduced without affecting seizure frequency.

LEV retention at 12 months

The group of 48 patients was not different from the remaining patients in terms of age, sex, epilepsy history, seizure frequency, and number of antiepileptic drugs administered (Wilcoxon sum rank test).

Table 1 Efficacy of LEV according to epilepsy syndromes

Epilepsy syndromes	No. of patients 81	Responders/seizure free
Focal epilepsy	30	11/6
Probably symptomatic	(12)	(7/4)
Symptomatic	(18)	(4/2)
West syndrome	17	6/3
Cryptogenic	(7)	(4/2)
Symptomatic	(10)	(2/1)
Lennox—Gastaut	2	0/0
Myoclonic-astatic	2	2/1
Eyelid myoclonia	2	1/0
Dravet's syndrome	3	1/0
Early myoclonic encephalopathy	6	0/0
Unclassifiable	19	3 (0)

Table 2 LEV efficacy according to epilepsy syndromes after a mean follow-up period of 3 and 12 months, respectively

Epilepsy syndromes	No. of patients 48	After a mean of 3 month (R/SF)	After a mean of 12 month (R/SF)	Loss of efficacy (%)
Focal epilepsy	18	9/5	5/2	44%
Probably symptomatic	(11)	(6/3)	(4/2)	(33%)
Symptomatic	(7)	(3/2)	(1/0)	(67%)
West syndrome	10	5/2	3/1	40%
Cryptogenic	(5)	(3/2)	(2/1)	(33%)
Symptomatic	(5)	(2/0)	(1/0)	(50%)
Lennox—Gastaut	2	2/0	0/0	100%
Myoclonic-astatic	2	2/1	1/1	50%
Dravet's syndrome	2	2/0	0/0	100%
Early myoclonic encephalopathy	2	0/0	0/0	—
Unclassifiable	7	2/0	0/0	100%

R: responders; SF: seizure free.

Efficacy retention at 12 months was observed in nine out of 48 patients (19%), of whom four (8%) remained seizure free (Table 2). Five of these patients (56%) were affected by focal epilepsy, three (33%) by West syndrome, and one (11%) by myoclonic-astatic epilepsy. A loss of efficacy was seen in thirteen (59%) of the 22 initial responders. With respect to epilepsy syndromes, efficacy loss was less obvious in patients with focal epilepsy (44%) and West syndrome (40%) (Table 2).

Safety

At least one adverse event was seen in 28 (34%) patients. The most common adverse events were drowsiness (45%), nervousness (36%), cognitive disturbances (29%), loss of appetite (14%), and sleep disturbances (7%). One patient (4%) presented with vomiting. Eight patients showed more than one side effect. No life threatening side effects were observed during the study and all side effects were either tolerable or resolved in time through dosage reduction or discontinuation of the drug. There were no significant laboratory anomalies in liver function, renal function, or hematology.

Discussion

Controlled and open-label studies showed the efficacy of LEV in a wide range of seizures and epilepsies in children and adults.[6—8,12—18] In a study designed to evaluate short-term efficacy and tolerability of LEV, Glauser et al.[8] found that giving LEV to children with partial seizures led to a statistically greater reduction in partial seizures, with 44.6% of children responsive to LEV showing more than a 50% drop in seizures with seven (6.9%) becoming seizure free.

Prospective, open-label studies showed that LEV effectively improves seizure control as an add-on drug for resistant epilepsy in childhood.[19,20] Opp et al.[19] noted that 24.9% of 209 children were responders, with more than 50% of seizure reduction during LEV therapy. In a previous study, we observed higher responder rates after a mean follow-up period of 7 months, LEV being effective in 39% of children, with 8% of patients becoming seizure free.[20] Similar findings were observed by Lagae et al.[21] in a study of 67 children. These authors noted that 90% of children placed under LEV alone were responders. Seizure frequency before and after 12 months of LEV therapy was also evaluated in 59 children affected by intractable epilepsy.[22] The authors found that the response rate at 12 months was 52%, with 22% of patients being seizure free. Lower responder rates (29%) were observed by Koukkari et al.[21] in a retrospective study that included 52 children with refractory epilepsy.

LEV is currently approved in Italy for the treatment of patients older than 4 years of age with partial seizures and secondary generalized epilepsy. We believe this study is the first evaluation of the efficacy and safety of LEV in infants aged less than 4 years with epileptic seizures and epileptic syndromes. In an open-label, prospective study we previously reported that LEV was effective in controlling epilepsy in 16 infants in whom a higher responder rate was observed compared with rates seen in older children.[20] Moreover, a number of young children were treated with LEV and reported in other studies.[19—24] However, systematic data are not yet available. The design of the present study reflects daily clinical practice. Although this introduces some methodological weaknesses, it provides a more natural and realistic view of the use of LEV in

infants and young children. All patients we studied were refractory to first line drugs. The main aim of add-on treatment in these patients was to improve their quality of life by decreasing seizure frequency as much as possible and by limiting adverse events, rather than to make them seizure free.[24]

LEV efficacy was evaluated in relation to seizure types and to epilepsy syndromes. Thirty percent of patients had a more than a 50% reduction in seizure frequency after a mean follow-up period of 9 months. The percentage of responders was lower than that reported in older children in previous studies.[20,21–23] The lower response rates we observed may be because of insufficient experience with LEV in young children, resulting in a very strong selection bias for infants with very difficult-to-treat epilepsies. This bias is further enhanced in our data which are constituted by pooled data of the first experiences with LEV coming from six pediatric neurology departments. Although the patients we investigated did not have long histories of epilepsy, up to 10 AEDs had been used before LEV therapy was started. Moreover, the majority of children were mentally retarded, with epilepsy being mainly related to brain injuries or brain malformations. As in the previous studies involving older children, LEV resulted to effective in both focal epilepsy (46% of responders) and generalized epilepsy (42% of responders). In particular, good responses were also found in patients with West syndrome with six of 17 of such patients (35%) being classified as responders. This is a good result considering that the majority of patients exhibited refractive infantile spasms. Of course, further clinical trials are needed to determine the efficacy of LEV in these epilepsy syndromes. In fact, the size of our population was not so large to enable us to draw more definite conclusions.

We compared the efficacy in 48 patients observed after a mean of three months of follow-up with retention after 12 months of LEV, with regard to loss of efficacy. According to Krakow et al.[25] the retention rate is an important measure of the efficacy and adverse events of the drug because it is a reliable indicator over time. Nineteen percent of our patients were still responsive to LEV after a minimum of 12 months of follow-up. Loss of efficacy was observed in 59% of the initial responders. Although our series was small, a well-sustained LEV efficacy was observed in patients with focal epilepsy. Since comedication was not (or only slightly) altered before seizure relapse, we suggest that the loss of efficacy with LEV was likely related to the development of tolerance to the drug.

The mean dose of LEV in our study, 41 mg/kg per day, was similar to that used in studies on older children.[20,21,23] As clearance of LEV in young children is 30–40% greater,[5] it is possible that better results could be obtained with higher doses of LEV. However, previous studies did not find a relationship between LEV doses and efficacy.[2,20] Moreover, we found significantly higher doses in nonresponder patients than in responder patients (data not shown).

LEV has been reported to be a well-tolerated, relatively safe drug.[20] Adverse reactions, such as headache, somnolence, and anorexia, have incidences varying from 30%[20,21,23] to 44.9%.[19] Acute psychosis[26,27] and choreoathetosis[20] have also been reported. Hemorrhagic colitis lacking infectious etiology and severe apnea were reported in two children. In both patients symptoms reversed after LEV was stopped.[19] Side effects appear to be more frequent with high LEV doses (>40 mg/kg per day).[24] However, recent reports emphasized that LEV is well tolerated at doses up to 270 mg/kg per day.[22] Drowsiness, aggressiveness, and attention disorders represent the main side effects in patients treated with LEV.[20,24] Opp et al.[19] found that they were most frequent in children with physical handicaps or mental retardation. These authors suggested that this pediatric population should to be monitored carefully for adverse effects of LEV therapy. In the present study, adverse reactions were observed in 34% of patients and were usually limited to the titration period. As in previous reports,[20,22] somnolence and irritability were the most common adverse reactions, occurring in up to 28% of patients. However, in all patients the side effects were mild in severity and transient.

We conclude that although further studies of LEV monotherapy are required, the drug is safe and effective for a wide range of epilepsies and that it is a valid therapeutic option in infancy and early childhood.

References

1. Shorvon SD, van Rijckevorsel K. A new antiepileptic drug. *J Neurol Neurosurg Psychiatry* 2002;**72**:426–9.
2. Vigevano F. Levetiracetam in pediatrics. *J Child Neurol* 2005;**20**:87–93.
3. Niespodziany I, Klitgaard H, Margineanu DG. Levetiracetam inhibits the high-voltage-activated Ca(2+) current in pyramidal neurones of rat hippocampal slices. *Neurosci Lett* 2001;**306**:5–8.
4. Rigo JM, Hans G, Nguyen L, et al. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. *Br J Pharmacol* 2002;**136**:659–72.
5. Pellock JM, Glauser TA, Bebin EM, et al. Pharmacokinetic study of levetiracetam in children. *Epilepsia* 2001;**42**:1574–9.
6. Ben-Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial

seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. European Levetiracetam Study Group. *Epilepsia* 2000;**41**:1276—83.
7. Leppik IE, Biton V, Sander JW, Wieser HG. Levetiracetam and partial seizure subtypes: pooled data from three randomized, placebo-controlled trials. *Epilepsia* 2003;**44**:1585—7.
8. Glauser TA, Ayala R, Elterman RD, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology* 2006;**66**:1654—60.
9. Commission on classification and terminology of the International League Against Epilepsy, 1981. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;**22**:489—501.
10. Commission on classification and terminology of the International League Against Epilepsy, 1989. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**:389—99.
11. Engel Jr J International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001;**42**:796—803.
12. Genton P, Sadzot B, Fejerman N, et al. Levetiracetam in a broad population of patients with refractory epilepsy: interim results of the international SKATE trial. *Acta Neurol Scand* 2006;**113**:387—94.
13. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia* 2000;**41**:1179—86.
14. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;**55**:236—42.
15. Glauser TA, Pellock JM, Bebin EM, et al. Efficacy and safety of levetiracetam in children with partial seizures: an open-label trial. *Epilepsia* 2002;**43**:518—24.
16. Herranz JL, Rufo-Campos M, Arteaga R. Effectiveness and tolerability of levetiracetam in 43 children and adolescents with epilepsy. *Rev Neurol* 2003;**37**:1005—8.
17. Wheless JW, Ng YT. Levetiracetam in refractory pediatric epilepsy. *J Child Neurol* 2002;**17**:413—5.
18. De los Reyes EC, Sharp GB, Hale SE. Levetiracetam in the treatment of Lennox—Gastaut syndrome. *Ann Neurol* 2001;**50**(Suppl. 1):S108.
19. Opp J, Tuxhorn I, May T, et al. Levetiracetam in children with refractory epilepsy: a multicenter open label study in Germany. *Seizure* 2005;**14**:476—84.
20. Grosso S, Franzoni E, Coppola G, et al. Efficacy and safety of levetiracetam: an add-on trial in children with refractory epilepsy. *Seizure* 2005;**14**:248—53.
21. Lagae L, Buyse G, Ceulemans B. Clinical experience with levetiracetam in childhood epilepsy: an add-on and monotherapy trial. *Seizure* 2005;**14**:66—71.
22. Mandelbaum DE, Bunch M, Kugler SL, Venkatasubramanian A, Wollack JB. Efficacy of levetiracetam at 12 months in children classified by seizure type, cognitive status, and previous anticonvulsant drug use. *J Child Neurol* 2005;**20**:590—4.
23. Koukkari MW, Guarino EJ. Retrospective study of the use of levetiracetam in childhood seizure disorders. *J Child Neurol* 2004;**19**:944—7.
24. Lagae L, Buyse G, Deconinck A, Ceulemans B. Effect of levetiracetam in refractory childhood epilepsy syndromes. *Eur J Paediatr Neurol* 2003;**7**:123—8.
25. Krakow K, Walker M, Otoul C, Sander JW. Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology* 2001;**56**:1772—4.
26. Kossoff EH, Bergey GK, Freeman JM, Vining EP. Levetiracetam psychosis in children with epilepsy. *Epilepsia* 2001;**42**:1611—3.
27. Mula M, Trimble MR, Sander JW. Psychiatric adverse events in patients with epilepsy and learning disabilities taking levetiracetam. *Seizure* 2004;**13**:55—7.