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CASE REPORT

Levetiracetam in patients with generalised epilepsy and myoclonic seizures: An open label study

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Summary

Purpose: To evaluate the efficacy and tolerability of levetiracetam (LEV) as either 'de novo' (monotherapy) or 'add-on' therapy in patients with different generalised epilepsies characterised by myoclonic seizures from an observational study.
Methods: We evaluated 35 patients (21 female, mean age 24.7 years) with different types of generalised epilepsies (juvenile myoclonic epilepsy (JME), severe myoclonic epilepsy of infancy (SMEI), Lennox—Gastaut syndrome (LGS), myoclonic-astatic epilepsy (MAE), myoclonic absences (MA), benign myoclonic epilepsy in infancy (BMEI) and 4 patients had unspecified epileptic syndromes). Patients received LEV as de novo monotherapy or add-on therapy. Seizure frequency changes and adverse events were observed. Follow-up was conducted for a period of 12 months after treatment.
Results: Patients received LEV 2000—3000 mg/day as de novo ($n = 8$) and as add-on therapy. In total, 29 (82%) of the 35 patients achieved $\geq$50% seizure frequency reduction, 15 (42%) patients achieved seizure freedom while a further 14 (40%) patients achieved $\geq$50—99% seizure frequency reduction. Six (17%) patients discontinued LEV due to inefficacy or seizure worsening. Not even a single patient discontinued due to adverse effects.
Conclusions: Our results confirm that LEV as de novo (monotherapy) and add-on therapy at doses between 2000 and 3000 mg/day effectively reduces myoclonic seizure frequency in patients with generalised epilepsy. LEV was also well-tolerated.

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Introduction

Levetiracetam (LEV) is a novel antiepileptic drug recently approved in the United States for the treatment of partial epilepsies with or without secondary generalisation.[1] One year later, LEV was also approved in Europe with the same indication. LEV is very similar to piracetam which is commonly used in high doses to treat cortical myoclonus.[2] They are both pyrrolidone derivatives that share similar chemical structures but have distinct pharmacological profiles and uses.[2,3] Although LEV is chemically similar to piracetam, its mechanism of action is not yet clarified. However, animal models have shown that LEV antagonizes neuronal hypersynchronization during a seizure.[4] Furthermore, several studies have demonstrated that LEV also works in patients with generalised epilepsy and cortical myoclonus too.[4,5]

In this study, we aimed to evaluate the efficacy and tolerability of LEV as either 'de novo' (monotherapy) or 'add-on' therapy in patients with different types of generalised epilepsy characterised by myoclonic seizures.

Patients and methods

From September 2004, we recruited patients diagnosed of generalised epilepsy who visited the epilepsy clinic, University of Catanzaro for an open study. The study group consisted of 35 patients (mean age 24.7 ± 10.5; 21 females). The study was approved by the University Hospital Ethics Committee, and all subjects and their guardians in case of children, granted informed consent to participate.

In all patients the diagnosis of generalised epilepsy was based on the International Classification of Epilepsies.[6] All clinical records were analyzed. The following clinical characteristics were noted: sex, age, AEDs used prior to LEV, age of epilepsy onset, frequency of seizures, abnormal neurological examination, family history of epilepsy, laboratory findings. Seizure types were identified according to the classification of epileptic seizures and syndromes by the International League Against Epilepsy.[6] All patients underwent several interictal electroencephalograms (EEG) including routine awake and sleep EEGs. Some of the patients had a clinical MRI (1.5 T) examination done, based on a protocol routinely used for patients with epilepsy, including T2-weighted images, and a coronal 3D sequence with contiguous slices, with and without administration of gadolinium.

LEV was started at the dose of 500 mg/day and was progressively increased to a mean dose of 2000–3000 mg/day. Only three patients (the youngest ones) received a lower dose of LEV between 1000 and 1500 mg daily. The mean dose was reached within 4 weeks. Patients were clinically observed every 3 months. First of all we observed the side effects and tolerability of LEV. Secondly, the efficacy was assessed by measuring changes in seizure frequency, especially myoclonic jerks. The basis for comparison was defined as the myoclonic seizure frequency in the 6 months prior to the commencement of treatment. We classified patients post-treatment into three categories: those achieving seizure freedom, those achieving between 50 and 99% reduction in seizures, and those with worsening. Two trained epileptologists were asked to grade the seizures.

We observed the reduction of massive or focal epileptic myoclonus and other generalised seizures (e.g. absence, tonic–clonic).

Results

Clinical characteristics of patients are summarized in Table 1. In details, 21 out of 35 (18 females) had juvenile myoclonic epilepsy (JME); four (males) had severe myoclonic epilepsy of infancy (SMEI); two (females) had Lennox–Gastaut syndrome (LGS); one

Table 1 Patient characteristics

Total patients	*n* = 35
Characteristics	
Sex	*N* (%)
Female	21 (60.0)
Male	14 (40.0)
Age	Years
Mean (±S.D.)	24.7 (10.6)
Median	26
Range	3–44
Type of epilepsy	*N* (%)
Juvenile myoclonic epilepsy (JME)	21 (60.0)
Severe myoclonic epilepsy of infancy (SMEI)	4 (11.4)
Lennox–Gastaut syndrome (LGS)	2 (5.7)
Benign myoclonic epilepsy in infancy (BMEI)	1 (2.9)
Myoclonic-astatic epilepsy (MAE)	1 (2.9)
Myoclonic absences (MA)	1 (2.9)
Unspecified	5 (14.3)
Age of seizure onset	Years
Mean (±S.D.)	8.9 (6.1)
Median	10
Range	0.25–21

(male) had myoclonic-astatic epilepsy (MAE); one (male) had myoclonic absences (MA), and one (male) had benign myoclonic epilepsy in infancy (BMEI). The remaining five patients (2 males) had unspecified epileptic syndromes. In details, all patients had myoclonic seizures; 11 patients had also generalised tonic–clonic seizures, two patients had also absences and seven had both.

Out of 35, eight (22.9%) patients received LEV as de novo monotherapy while 27 (77.1%) as add-on therapy to other drugs (e.g. lamotrigine, valproate). All eight patients who received LEV monotherapy had JME.

Patients received LEV treatment for a mean of 34.06 (±12.74) months and followed up at 28.4 months on average (range 5–52). As shown in Fig. 1, 29 (83%) patients demonstrated a ≥50%

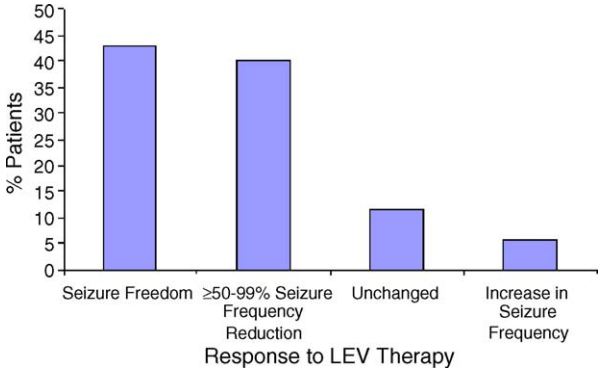

Figure 1 The percentage of patients who responded to LEV therapy.

Table 2 Details of baseline therapy and response to LEV treatment in patients receiving add-on therapy (n = 27), by epilepsy type

Type of epilepsy	AED therapy at baseline	No. of seizures/ month	Reason for add-on therapy	Age add-on (year)	Response to LEV therapy
JME	LTG	5	Dysmenorrhoea	24	Seizure freedom
JME	VPA	4	Encephalopathy	32	Seizure freedom
JME	LTG	7	Poor efficacy	32	Seizure freedom
JME	LTG	7	Poor efficacy	17	Seizure freedom
JME	LTG	6	Poor efficacy	25	Seizure freedom
JME	LTG	7	Poor efficacy	38	Seizure freedom
JME	VPA + ACZ	5	Tremor (VPA)	2	Seizure freedom
JME	VPA + LTG	8	Poor efficacy (LTG), dysmenorrhea (VPA)	36	Seizure freedom
JME	LTG	7	Poor efficacy	19	≥50–99% seizure reduction
JME	PB + PHT + TPM	6	Poor efficacy (LTG), tremor (VPA)	15	≥50–99% seizure reduction
JME	LTG + CZP + PB	5	Poor efficacy (LTG + CZP)	29	≥50–99% seizure reduction
JME	VPA	5	Poor efficacy	28	No change
JME	PB + CZP + ACZ	6	Poor efficacy (CZP, ACZ, PB)	19	Increase in seizures
SMEI	VPA + CZP	6	Poor efficacy	7	≥50–99% seizure reduction
SMEI	VPA + CZP	7	Poor efficacy (VPA)	8	≥50–99% seizure reduction
SMEI	LTG + PB + CBZ	4	Poor efficacy (LTG)	7	≥50–99% seizure reduction
SMEI	VPA + PB + ACZ + CZP	8	Poor efficacy (VPA + CZP + ACZ)	9	No change
LGS	PB + TPM + CBZ	5	Action tremor	9	≥50–99% seizure reduction
LGS	VPA + CZP + CBZ	7	Poor efficacy (VPA + CZP)	11	Increase in seizures
BMEI	VPA	5	Hyperammonemia	6	Seizure freedom
MAE	VPA + LTG	6	Poor efficacy (VPA)	9	≥50–99% seizure reduction
MA	VPA + TPM	5	Poor efficacy (VPA)	13	≥50–99% seizure reduction
Unspecified	LTG + VPA	5	Poor efficacy	33	Seizure freedom
Unspecified	PB + TPM	4	Poor efficacy	31	≥50–99% seizure reduction
Unspecified	LTG + CZP + VPA	4	Poor efficacy (LTG)	27	≥50–99% seizure reduction
Unspecified	VPA + PB + PHT	6	Hair loss (VPA)	23	≥50–99% seizure reduction
Unspecified	VPA	5	Poor efficacy	22	≥50–99% seizure reduction

ACZ, acetazolamide; CBZ, carbamazepine; CZP, clonazepam; LTG, lamotrigine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproic acid.

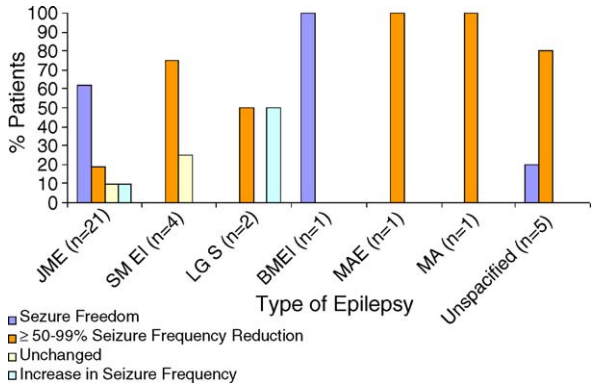

Figure 2 The efficacy (% of seizure reduction) of LEV treatment by epilepsy type.

seizure frequency reduction, comprising six of eight (75%) patients who received LEV monotherapy and 23 on 27 (85%) patients who received LEV add-on therapy. Of these 35 subjects, 15 (43%) patients achieved seizure freedom and a further 14 (40%) patients showed a seizure frequency reduction of ≥50—99%.

Seizure frequency following LEV therapy remained unchanged in four (11.4%) out of 35 patients and worsened in two (5.7%) patients.

Of the eight patients who received LEV monotherapy (all JME), five (62.5%) patients achieved seizure freedom and one (12.5%) demonstrated a ≥50—99% seizure frequency reduction; seizure frequency remained unchanged in one (12.5%) patient and worsened in one (12.5%) patient.

The response of patients who received LEV add-on therapy (n = 27), and the reasons for add-on therapy, are shown in Table 2. Ten of 27 (37%) patients who received add-on therapy achieved seizure freedom and 13/27 (48.1%) patients demonstrated a ≥50—99% seizure frequency reduction whereas seizure frequency remained unchanged in two (7.4%) patients and worsened in two (7.4%) patients (Table 2).

The efficacy of LEV treatment by epilepsy type is shown in Fig. 2. No changes on interictal EEGs were observed.

Six out of 35 (17.1%) patients discontinued LEV treatment. Reasons for discontinuation were lack of efficacy (n = 4) and worsening in seizure frequency (n = 2). No patients discontinued treatment due to AEs.

Discussion

LEV is chemically related to piracetam which has been previously used to treat cortical myoclonus but its mechanism of action is not yet clarified. Recent studies reported the efficacy of LEV in the treatment of myoclonus and progressive myoclonic epilepsies.[2—10] These studies showed that LEV is very well-tolerated in adults and children even at high doses.[2—10] Our study further supports this knowledge and reinforces the concept that LEV works very well in the treatment of epileptic myoclonus.

We observed for several months 35 consecutive patients referring to our Institute with different types of epilepsy but all characterised by prominent myoclonic seizures. We used LEV at common dosage between 2000 and 3000 mg/day with the exception of three young patients. Myoclonus dramatically responded to the LEV and indeed a total of 29 patients obtained seizure reduction. Of these, 15 patients achieved seizure freedom and 14 patients experienced ≥50—99% seizure frequency reduction. The seizure frequency reduction and in particular the antimyoclonic efficacy was greatest among patients with JME that assumed either de novo or add-on LEV therapy. On the other hand, the unchanged or worsened seizure frequency was greater in patients with refractory generalised epilepsy (SMEI and LGS). Our results may represent an interesting point because LEV might be a very good alternative to other antiepileptic drugs such as lamotrigine used in the treatment of idiophatic myoclonic seizures and furthermore useful in females. In fact, it is very well-known in the literature that lamotrigine is now widely used as a substitute for sodium valproate in the treatment of young female patients who either had sodium valproate side effects (e.g. ovarii polycystic) or did not tolerate the drug.[11] To date, there are no reports of endocrinological problems or menstrual issues with LEV.[12] Thus, our results further confirm that LEV could be tried as the first drug in young female epileptic patients specially for JME.

Overall, our results confirm that LEV as de novo (monotherapy) and add-on therapy at doses between 2000 and 3000 mg/day effectively reduces myoclonic seizure frequency in patients with idiopathic generalised epilepsy.

References

1. Frucht SJ, Fahn S. The clinical spectrum of posthypoxic myoclonus. *Mov Disord* 2000;**15**(Suppl. 1):2—7.
2. Frucht SJ, Louis ED, Chuang C, et al. A pilot tolerability and efficacy study of levetiracetam in patients with cronic myoclonus. *Neurology* 2001;**57**:1112—4.
3. Crest C, et al. Levetiracetam in progressive myoclonic epilepsy. An exploratory study in 9 patients. *Neurology* 2004;**62**: 640—3.
4. Krauss GL, et al. Suppression of post-hypoxic and post encephalitic myoclonus with levetiracetam. *Neurology* 2001;**56**: 411—2.

5. Kinrions P, et al. Efficacy of levetiracetam in a patient with Unverricht-Lundborg progressive myoclonic epilepsy. *Neurology* 2003;**60**:1394.
6. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981;**22**:489—501.
7. Magaudda A, Gelisse P, Genton P. Antimyoclonic effect of Levetiracetam in 13 patients with Unverricht-Lundborg disease: clinical observations. *Epilepsia* 2004;**45**(6):678—81.
8. Goldestein JL. Levetiracetam: exacerbation of epilepsy. *Epilepsia* 2001;**42**(7):254.
9. Montorius GD, Lippman SM, Rosenfield WE. Exacerbation of seizures: any relationship to dose escalation of levetiracetam (Keppra)? *Epilepsia* 2001;**42**(7):184.
10. Genton P, Gelisse P. Antimyoclonic effect of levitiracetam. *Epileptic Disord* 2000;**2**:209—12.
11. Cunnington M, Tennis P. International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005;**64**(6): 955—60.
12. Johannessen SI, Helde G, Brodtkorb E. Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia* 2005;**46**(5):775—7.