Levetiracetam in absence epilepsy

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The aim of the study was to assess the efficacy, tolerability, and safety of levetiracetam therapy in children and adolescents with absence epilepsy. Twenty-one participants (11 male, 10 female) with typical absence seizures were enrolled in this prospective study from seven centres in Italy. The mean age and age range at time of enrolment into the study were 8 years 9 months (SD 0.9) and 5 years 1 month to 13 years respectively. All patients were carefully evaluated at 6 months from baseline, and 12 patients were also re-evaluated at 12 months after the beginning of therapy with levetiracetam. At the 6-month evaluation, out of 21 patients studied, 11 were seizure free and one showed 'decreased' seizures (more than 50% reduction in seizures). A less than 50% reduction in seizures was observed in nine patients. At the 12-month evaluation, 10 patients were completely seizure free and two were seizure free with some anomalies in electroencephalograms. Two patients who had shown no improvement at 6 months had decreased seizures at the second follow-up. Our results suggest that monotherapy with levetiracetam could be effective and well tolerated in patients with childhood absence epilepsy and juvenile absence epilepsy. Prospective, large, long-term double-blind studies are needed to confirm these findings.

See end of paper for list of abbreviations.

Typical absences are the defining seizure type of childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE).[1] These two syndromes are part of the idiopathic generalized epilepsies according to the proposed diagnostic scheme from the Report of the International League Against Epilepsy Task Force on Classification and Terminology.[2] These types of epilepsy are generally associated with normal neurological development and respond to antiepileptic drugs (AEDs). It is generally considered a benign type of epilepsy, although complete remission is not achieved in about 19% of patients.[3] In patients with absence seizures, neuropsychological studies have documented cognitive dysfunction that improved after seizures had stopped.[4] Many AEDs are available to physicians for the treatment of absence seizures; generally this form of epilepsy needs treatment because absences are very frequent throughout the day. It is generally agreed that valproic acid, ethosuximide and, more recently, lamotrigine are the most effective AEDS in CAE and they are considered the first-line agents.[3,5–7] It is important to remember that valproic acid can often cause significant endocrine problems (such as weight gain, alopecia, menstrual irregularities, and polycystic ovary syndrome) that can disturb the quality of life of patients, and in particular adolescent patients.[8,9]

Lamotrigine is effective in the treatment of typical absence seizures (TAS) but it too must be used with caution because of its side effects, in particular severe dermatological reactions.[6]

Levetiracetam (LEV) might be a good alternative because several reports and open label studies have pointed out its efficacy in generalized epilepsy.[10–14] There are very few data about this type of epilepsy. Furthermore, the pharmacokinetic profile of LEV makes this AED a good option for the treatment of paediatric patients.[15,16]

In this study we sought to evaluate the efficacy and tolerability of LEV as de novo monotherapy in patients with CAE and JAE.

Method

This was a multicentre, prospective, long-term, open-label treatment study evaluating a large group of patients with absence epilepsy.

Twenty-one participants (11 male, 10 female) with TAS were enrolled in this prospective study from seven centres in Italy. All had been diagnosed with this type of epilepsy, according to International League Against Epilepsy criteria.[1] The age at seizure onset ranged from 5 years 1 month to 13 years (mean 8y 9mo [SD 0.9]). All patients were newly diagnosed with this type of epilepsy. Exclusion criteria were as follows: neurological disorders or intellectual impairment, history or presence of pseudoseizures, history of recurrent psychotic or major affective disorder, the use of medication affecting the central nervous system unless patients had been stabilized on such medication for more than 1 month before the study, metabolic disorders, active infection or neoplasm, any clinically relevant progressive or serious illness expected to interfere with the ability of the patient to complete the trial, previous treatment with other AEDs, and discontinuation of LEV as a result of adverse events. Inclusion criteria were the following: CAE and JAE diagnosis obtained as a result of clinical evaluation, newly diagnosed patients (onset

of disease), and specific electroencephalogram (EEG) abnormalities (ictal discharges of generalized high-amplitude spike and double spike and slow-wave complexes that were rhythmic at about 3 to 4Hz).

Before starting LEV, all patients gave informed consent and the study was approved by local ethics committees. All patients began on LEV 250mg each evening, and dosing was escalated gradually. Dosage modifications were made in increments of 250mg daily every 2 weeks, depending on clinical response and adverse effects. After titration, the range of prescribed LEV dosages administered ranged from 1000 to 2000mg daily. When freedom from seizures was attained at any dose, no further modification was made to the regimen. In non-responding patients, the LEV dosage was increased to 70mg/kg/day if no side effect was observed. All patients were carefully evaluated at 6 months from baseline; 12 patients were evaluated again at 12 months after the start of LEV therapy.

At each visit, the investigator assessed the adverse events and the number and type of seizures, with their severity, relationship to LEV treatment, and outcome. Standard forms were used to collect numbers of seizures and to document adverse effects. Each treatment-emergent physical and neurological abnormality was recorded as an adverse event, as was any worsening of the condition or requirement for medication. Height and weight were monitored throughout the trial.

Physical and neurological examinations, laboratory assessment, and electrocardiography were performed, and vital signs were recorded at baseline and during the follow-up; detailed records were kept of adverse events.

During the follow-up the following laboratory examinations were performed on all patients: complete peripheral blood counts, urinary analysis and measurement of blood creatinine, alanine and aspartate aminotransferase levels, erythrocyte and leukocyte count, amylase, transaminase, and blood urea nitrogen.

Participants could be withdrawn from the study in any of the following circumstances: parent withdrew consent, participant experienced an adverse event, dose schedule was not tolerated, compliance was not maintained, or participant could not remain in contact with their hospital.

Patient evaluation started at the end of LEV titration. The efficacy of LEV therapy was calculated by counting the mean seizure frequency per month. The response to LEV treatment was classified as seizure free (100% seizure control), responders (individuals with more than 50% reduction in monthly seizure frequency) or non-responders (less than 50% reduction).

Seizure freedom and seizure reduction rates were evaluated at 6 and 12 months. Patient characteristics and study results are reported with descriptive statistics (mean [SD] or percentages, as appropriate).

Results

All patients remained on LEV treatment throughout the study.

EFFICACY

Table I shows changes in seizure frequency at 6 and 12 months of follow-up. At 6 months, out of 21 patients studied, 11 were seizure free and one showed a more than 50% reduction in seizures. No response (less than 50% reduction of seizures) was observed in nine patients. Five of six patients with an onset of TAS more than 10 years previously were non-responders.

Table I: Clinical and EEG characteristics of the patients studied

Patient no.	*Sex*	*Age (y:m)*	*Family history*	*Dose of LEV (mg/kg/day)*	*Follow-up after LEV therapy*			
					6mo		*12mo*	
					Seizures	*EEG*	*Seizures*	*EEG*
1	M	13:2	No	51	NR	+		
2	F	9:0	No	35	SF	N		
3	F	5:1	No	68	SF	+		
4	F	8:6	No	65	SF	+	SF	+
5	F	6:0	No	70	NR	+		
6	M	5:8	No	50	SF	N	SF	N
7	M	6:8	No	60	SF	N	SF	N
8	F	6:3	No	48	SF	N	SF	N
9	F	6:9	No	45	SF	N		
10	F	11:2	No	50	NR	+		
11	M	9:8	Yes	34	NR	+		
12	M	6:7	No	38	NR	+	Responder	N
13	M	8:7	No	40	SF	N	SF	N
14	M	9:2	No	66	SF	N	SF	N
15	M	9:8	No	65	NR	+		
16	M	10:3	No	50	SF	N		
17	M	11:0	No	45	NR	+	SF	+
18	F	8:6	No	38	SF	N	SF	N
19	F	9:3	Yes	64	Responder	+	SF	N
20	M	11:1	No	31	NR	+	Responder	
21	F	10:1	No	57	NR	+	SF	

EEG, electro encephalogram; LEV, levetiracetam; NR, non-responders (less than 50% reduction in monthly seizure frequency); N, normal; SF, seizure free; +, presence of spike-and-wave complexes; responder, more than 50% reduction in monthly seizure frequency.

Twelve patients were re-evaluated at 12 months: at this evaluation, 10 patients were completely seizure free, and two were seizure free with sporadic spike-wave complexes during hyperventilation at EEG. Two patients who were non-responders at 6 months moved to became responders at the second follow-up.

Finally, we compared the demographics and clinical characteristics of the seizure-free and non-responder patients but we failed to find a difference between these two groups. No patient developed other types of seizure during the study.

TOLERABILITY

No adverse reaction occurred in any patient during the study; no findings (in particular in physical and neurological examinations and psychiatric and mental status) of major clinical significance was noted. Only two patients reported transient somnolence and irritability. No change from baseline in laboratory values was found in laboratory test results, vital signs, or electrocardiographic recordings. The 12 patients who were followed for 12 months did not report any significant side effects either.

Discussion

LEV is a novel AED: its mechanisms of action seem to be different from those of other AEDs.[17] LEV binds to a specific membrane binding site in the brain,[18] it does not affect glutamate or γ-aminobutyric acid-mediated synaptic transmission,[19] and it does not modulate voltage-dependent sodium or T-type calcium currents.[20] LEV binds to a specific binding site in the brain for synaptic vesicle protein SV2A and acts by modulating the function of SV2A.[21] The antiepileptic mechanism of action of LEV is related to effects on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor channels in mouse cortical neurons in culture.[22]

LEV is a new AED that has proved to be effective both as monotherapy and adjunctive therapy in the treatment of generalized epilepsies.[6,10–14] In particular, Di Bonaventura et al.[10] used LEV to treat 19 patients with primary generalized epilepsy; four of them had CAE. After a follow-up of 6 months, three patients were seizure-free and one showed a 50 to 75% reduction in seizures. In all except one patient, normal EEGs were achieved. These authors suggest that this AED is effective in treating this form of generalized epilepsy. Our study is the first trial of LEV in absence epilepsy and it suggests that the LEV as monotherapy is effective and well tolerated in newly diagnosed patients with CAE and JAE. In fact, overall, at the 6-month follow-up, 12 children achieved a 50% or greater response. It is interesting that the patients re-evaluated at 12 months showed an improvement in seizure control. This improvement could have been the result of spontaneous remission because there are fluctuations in seizure frequency in epileptic patients; however, our experience shows that LEV monotherapy, as a first drug, can be effective in this type of epilepsy. Moreover, EEG abnormalities disappeared or decreased markedly in most of our patients during treatment with LEV; this fact, which is in general agreement with clinical response, confirms that this AED could be considered a valuable new agent.

Absence epilepsy has been scrutinized by many researchers studying animal models of this type of epilepsy; it has been demonstrated that absence seizures could originate from restricted regions of the cerebral cortex.[23] One study demonstrated the ability of LEV to reduce the pattern of hyperexcitability that occurs in a genetic animal model of absence seizure;[24] more recently, these data have been confirmed by Marrosu et al.,[25] who demonstrated that LEV attenuates spontaneous spike-and-wave discharges in epileptic DBA/2J mice.

In our study the tolerability of LEV was uniformly good and no one dropped out as a result of adverse events, confirming previous data about the safety of this drug.[10,11,15,26] With regard to safety, LEV has been reported to be well tolerated. Adverse reactions, mainly headache, infection, somnolence and anorexia, have been reported, with the incidence varying from 10 to 30%.[27,28] Sedation and acute psychosis have also been reported.[29–32] In our study, LEV was well tolerated: in fact, only two patients reported transient somnolence and irritability. Somnolence, dizziness, and headache were the three most frequent events in the large study performed by Tsai et al.[33] However, no significant laboratory abnormality developed in any patient. Our lower than previously reported behavioural side effects could be related to the fact that all participants had an idiopathic epilepsy and that the final dosage of LEV was not high; moreover, all our patients were treated with monotherapy; this fact could also explain the lack of side effects because it is well known that adverse effects are increased in patients taking multiple AEDs in comparison with those taking a single agent. Furthermore, the number of AEDs taken concurrently in other trials could have had an effect on the retention rates, because patients on LEV monotherapy are more likely to continue the AED. Our study shows the high retention rate of LEV, confirming the safety of this AED. This novel AED has pharmacokinetic characteristics that have been described as close to ideal;[34] LEV has a high oral bioavailability that is unaffected by food, shows linear kinetics, is not significantly bound to plasma proteins, and is not prone to pharmacokinetic drug interactions.

Conclusion

The present study confirms that LEV represents a valuable AED and suggests its utility in the treatment in patients with newly diagnosed CAE and JAE as it does not cause significant side effects. The place of LEV in the treatment of this type of epilepsy will be more clearly defined over the coming years, as experience from further trials and routine clinical use continues to accumulate.

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List of abbreviations

AED	Antiepileptic drug
CAE	Childhood absence epilepsy
JAE	Juvenile absence epilepsy
TAS	Typical absence seizures