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Loss of the initial efficacy of levetiracetam in patients with refractory epilepsy

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ABSTRACT

Purpose: The efficacy and safety of the anti-convulsive drug levetiracetam (LEV) has been well documented but few clinical studies have investigated tolerance to LEV. The aim of this study was to evaluate the loss of the initial efficacy of LEV in adult patients with refractory partial-onset seizures.
Methods: We enrolled patients with refractory partial epilepsy who were started on add-on LEV treatment. The efficacy of LEV was evaluated every three months and the seizure frequency was decided by the average number of monthly seizures. A responder was defined as a patient with a $\geq$50% reduction in seizure frequency from the baseline. Seizure freedom was defined as a seizure-free status from the beginning of LEV treatment to the evaluation period. Loss of the initial efficacy was defined as a shift from responder status during the first three months of LEV treatment to non-responder status during the follow-up period.
Results: A total of 95 epilepsy patients were analyzed. During the first three months of LEV treatment, 50 (52.6%) of the 95 patients were responders with a $\geq$50% seizure reduction. Nine patients (18.0%) showed a loss of initial efficacy during the second three-month period. In contrast, only two (4.0%) of the non-responders during the first three months became responders during the next three months. However, this difference did not reach statistical significance ($P = 0.054$). Based on Kaplan–Meier survival estimates, 49.2% of the patients who initially responded to LEV treatment during the first three months were predicted to lose this response at 42 months. Loss of the initial efficacy of LEV treatment occurred mostly within 18 months.
Conclusion: This study suggests that the occurrence of tolerance is more common than late gain of efficacy of treatment although larger prospective studies would have to be carried out to prove this observation.

1. Introduction

Drug tolerance can be defined as a decrease in susceptibility to the effects of a drug due to its continued administration.[1] Several hypotheses have been suggested to explain the development of tolerance. The overexpression of multidrug transporters at the blood–brain barrier is considered to be one factor in this phenomenon.[2] Based on previous data from animal experiments, many antiepileptic drugs (AEDs) have been demonstrated to be substrates for multidrug transporters and to show reduced antiepileptic efficacy due to tolerance development after repeated administration.[1]

The efficacy and safety of the anti-convulsant levetiracetam (LEV), which has a novel structure and unique mechanisms of action, have been demonstrated in many clinical studies. In addition, several studies have shown sustained long-term efficacy of LEV as an add-on therapy.[3–8] Pooled data[9] in patients with refractory epilepsy treated with LEV during the development program showed that no tolerance build up to LEV occurs. However, several animal studies have reported the development of tolerance to LEV.[10–12] A recent study using rats with chronic epilepsy revealed that LEV treatment led to effective seizure control but, despite the fact that adequate serum and brain levels of LEV were maintained, efficacy was lost within a week.[12] Incidental evidence also shows that tolerance to LEV can occur in humans; French et al.[3] have reported that the mean proportion of seizure-free days is higher in the first week of LEV treatment than in subsequent weeks, suggesting tolerance development.

It is important to further investigate whether tolerance to LEV occurs in human patients. There have been few clinical studies to date that have addressed this. In most previous studies on the efficacy of LEV, efficacy was evaluated at a certain time period without considering those patients who were initial non-responders but became responders later. Furthermore, no discrimination between lack and loss of efficacy was performed. Accordingly, the aim of our present study was to evaluate loss of initial efficacy of LEV in adult patients with refractory partial-onset seizures.

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2. Material and methods

2.1. Subjects

Patients aged at least 18 years with refractory partial epilepsy who were started on add-on LEV treatment between January 2007 and September 2010 were enrolled in this study. Subjects were included if they had been receiving one or more concomitant AEDs at stable doses for at least four weeks prior to selection, if they had uncontrolled partial seizures with or without secondary generalization at least once a month during the three-month retrospective baseline period before LEV commencement, if their epilepsy duration was at least two years from seizure onset, and if they were followed up for more than six months from LEV treatment initiation. Subjects were excluded if they had started on other AEDs simultaneously with LEV or within six months of LEV initiation, if they discontinued concomitant AED within six months of commencing LEV therapy, if they had an epilepsy surgery one year prior to commencing LEV therapy, if they had severe medical and psychiatric disorders, or if their seizure frequency could not be counted. All of the patients included in the study had been regularly monitored by one of four physicians, each a co-author of this study.

A standardized data form was developed and the data were obtained retrospectively from individual patient medical records. Variables included in the database were: age, sex, age at onset, duration of epilepsy, history of epilepsy surgery, current co-morbidity, past medical history, epilepsy risk factors, number and dose of concomitant AEDs, seizure frequency, magnetic resonance imaging (MRI) results, and electroencephalographic (EEG) findings. Epilepsy and seizures were classified using the International League Against Epilepsy (ILAE) classification.

2.2. LEV treatment

The starting dose was typically 1000 mg per day, divided into two doses. The LEV dose was increased to 1500 mg or 2000 mg daily if the patient continued to experience seizures. If seizure control was not satisfactory and there were no side effects, the dose was increased to the maximum daily dose (3000 mg per day). Based on the patient's and physician's judgment, the LEV dose could be reduced or withdrawn.

2.3. Assessment

The efficacy of LEV was evaluated every three months from the beginning of treatment. The seizure frequency was decided by the average monthly seizure number during each three-month interval. A responder was defined as a patient with a $\geq$50% reduction in seizure frequency from the baseline seizure frequency at three months prior to commencing LEV. Seizure freedom was defined by a seizure-free status from the beginning of LEV treatment to the evaluation period. Loss of initial efficacy was defined as a shift from responder status during the first three months of LEV treatment to non-responder status during the follow-up period.

2.4. Statistical analysis

Statistical analysis was performed using PASW statistics 18.0 for Windows (SPSS, Chicago, IL). Parametric data are expressed as the mean $\pm$ standard deviation (SD). Comparisons between responders and non-responders groups were analyzed using binary logistic regression analysis. The difference between patients with loss of initial efficacy and gain of efficacy in the second three months was evaluated by Fisher's exact test. P values of <0.05 were considered to be statistically significant. A Kaplan–Meier survival curve was generated to analyze the loss of initial efficacy of LEV during the follow-up period.

Table 1
Basic patient characteristics.

Total number of patients (n)	95
Gender (male/female)	47 (49.5%)/48 (50.5%)
Age (years), mean $\pm$ SD	39.1 $\pm$ 10.8
Onset age (years), mean $\pm$ SD	17.3 $\pm$ 11.8
Duration of disease (years), mean $\pm$ SD	21.8 $\pm$ 11.2
Risk factors (n)	
Encephalitis	17 (17.9%)
Febrile convulsion	13 (13.7%)
Trauma with loss of consciousness	8 (8.4%)
Perinatal injury	8 (5.6%)
Stroke	6 (6.3%)
Previous epilepsy surgery (n)	Temporal lobectomy (5), Lesionectomy (2), VNS (2), DBS (2)
Number of other AEDs, mean $\pm$ SD	2.7 $\pm$ 1.1
1 concomitant AED (n, %)	9 (9.5%)
2 concomitant AEDs (n, %)	43 (45.3%)
3 concomitant AEDs (n, %)	21 (22.1%)
$\geq$4 concomitant AEDs (n, %)	22 (23.2%)
Seizure frequency at baseline (n/month)	5.4 $\pm$ 21.7
Seizure types (n)	
Simple partial	17 (17.9%)
Complex partial	75 (78.9%)
Secondary generalized	81 (85.3%)
Undetermined	3 (3.4%)
Type of epilepsy (n)	
Symptomatic	52 (54.7%)
Cryptogenic	43 (45.3%)

DBS: Deep brain stimulation, SD: standard deviation, VNS: vagus nerve stimulation.

3. Results

3.1. Patient characteristics

A total of 95 epilepsy patients were included in the final study cohort (Table 1). The mean seizure frequency of all seizure types during the baseline period was 3.5 $\pm$ 5.3 per month. All patients were taking AEDs at baseline with 9 (9.5%) taking one AED, 43 (45.3%) taking two AEDs, 21 (22.1%) taking three AEDs and 22 (23.1%) taking four or more AEDs. The mean final LEV dose was 1373 $\pm$ 546 mg/day.

3.2. Initial LEV efficacy

During the first three months of LEV treatment, 50 (52.6%) of the 95 patients were responders with a $\geq$50% seizure reduction. Age, age at seizure onset, duration of epilepsy, baseline seizure frequency, and LEV dosage did not differ between responders and non-responders. The number of concomitant AEDs was significantly higher in non-responders (3.0 $\pm$ 1.1) than responders (2.4 $\pm$ 1.0) (P = 0.004).

3.3. Loss of initial LEV efficacy during the second three-month period

Of the 50 identified responders during the first three months, the initial efficacy of LEV was lost in 9 (18.0%) cases during the second three-month period (Fig. 1). Age, age at seizure onset, duration of epilepsy, baseline seizure frequency, LEV dosage and number of concomitant AEDs did not differ between the response maintenance group and those that lost initial LEV efficacy. Of the 45 non-responders recorded during the first three months, only two patients became responders during the second three-month period. In both of these cases, LEV doses were increased from 1000 mg/day to 2000 mg/day at three or four months from LEV commencement. Patients with loss of initial efficacy (9/50, 18.0%)