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Original article

The efficacy of levetiracetam for focal seizures and its blood levels in children

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Abstract

Aim: To evaluate the efficacy of levetiracetam (LEV) and the usefulness of measurement of its blood levels during the follow-up of patients with focal seizures.

Methods: Twenty-four patients (13 cases without impairment of consciousness or awareness and 11 cases with them or evolving to a bilateral, convulsive seizure) treated with LEV had their peak blood levels measured. The blood concentrations were measured at 2 weeks, 1 year and 2 years after reaching the LEV maintenance dosage. The efficacy of LEV was evaluated with repeated blood sampling to determine the seizure reduction rate. The patients were classified as effective cases (seizure reduction rate $> 50\%$) and ineffective cases ($\leqslant 50\%$).

Results: In Japanese children treated with LEV, the dosage and blood level showed positive correlations. The blood levels were higher in effective cases than in ineffective cases at all time points ($p < 0.05$). In effective cases, the blood concentration was 23.26 ± 6.88 μg/mL (mean ± SD) 2 weeks later, 23.59 ± 8.23 μg/mL 1 year later, and 24.46 ± 7.57 μg/mL 2 years later. However, the blood levels and efficacies showed positive correlations only at 2 weeks and 1 year later. No patients had any side effects.

Conclusions: No precise definition of the therapeutic range was possible because of the incomplete correlation between the blood level and seizure frequency. Instead of a therapeutic range, we recommend an optimal range for LEV of 20–30 μg/mL as a therapeutic target without any side effects.

Keywords: Antiepileptic drug; Maintenance dosage; Optimal range; Seizure reduction rate; Side effect

1. Introduction

Levetiracetam (LEV) was developed as a new substance that acted on the central nervous system in Belgium in the 1980s. LEV is an antiepileptic drug (AED) with a unique preclinical and pharmacological profile. LEV demonstrates no activity in acute seizure models but exhibits effective seizure protection in kindling animals of generalized epilepsy as chronic epilepsy models and models of chemoconvulsant-induced partial seizures [1]. Moreover, LEV has been known to bind to a unique binding site in the brain, the synaptic vesicle protein SV2A. It has been suggested that the function of this protein is to modulate synaptic vesicle fusion and the consequent release of neurotransmitter into the synapse [2]. Therefore, it was suggested that LEV was an AED having a new mechanism of action, and LEV has been administered as an antiepileptic drug for focal seizures in America since 1999. In Japan, it was approved for children with partial seizures in June, 2013.

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Measuring LEV blood levels helps optimize the dosage and reduce the side effects. However, the value of measurement has yet to be established. The correlation between the dosage and blood concentration has been proven [3], but some studies failed to show a relationship between the blood levels and efficacy or toxicity [4,5]. LEV does not affect the blood level of other AEDs because it does not induce or inhibit drug metabolizing enzymes in the liver [6–10], and its pharmacokinetic profile closely approximates the ideal characteristics [11]. The dosage for epilepsy in children and adolescents has been reviewed [12,13]. There were some opinions that the dosages for effective cases were bimodal [14], and high initial dosages were effective [15,16]. It is also necessary to investigate the upper range of the blood level. There are no strict criteria for the therapeutic range of the blood level at present. Therefore, we attempted to establish the optimal range of LEV as the therapeutic target. Twenty-four patients who experienced focal seizures and were treated with LEV were investigated in this study. The long-term efficacy of LEV and the usefulness of the blood level measurements were evaluated.

2. Methods

2.1. Patient selection and treatment

Twenty-four patients (15 males, 9 females; age range 0.7–16.7 years; mean age 9.8 years) were given LEV to treat focal seizures in the Pediatric Department of Kitasato University Hospital between January 2011 and December 2012. These patients included 13 cases without impairment of consciousness or awareness and 11 cases with impairment of consciousness or awareness or evolving to a bilateral, convulsive seizure. Their diagnoses were "benign epilepsy with centrotemporal spikes", "epilepsies attributed to and organized by structural-metabolic causes", and "epilepsies of unknown cause". And they were randomly selected for a prospective study. All patients and their parents were informed about the procedure and the purpose of the study, and they all agreed to participate. Eligible patients were diagnosed based on the "Report of the ILAE commission on classification and terminology, 2005–2009" due to their clinical seizure type, electroencephalogram, and either cranial computed tomography or magnetic resonance imaging. All patients had already taken some AEDs before starting LEV. Diagnoses categorized by age at onset and concomitant AEDs are shown in Table 1.

The LEV blood concentrations were measured at 2 weeks and 1 and 2 years after reaching the maintenance dose. The subjects were divided into effective cases (seizure reduction rate $> 50\%$) and ineffective cases ($\leqslant 50\%$). There were no cases that discontinued or tapered the LEV medication due to side effects or other problems. Moreover, it was easy to adjust other concomitant AEDs because LEV had no interactions with other drugs. Therefore, ineffective cases could continue the LEV medication for 2 years.

Table 1
Patients' characteristics according to diagnosis.

	Benign epilepsy with centrotemporal spikes	Epilepsies attributed to and organized by structural-metabolic causes	Epilepsies of unknown cause
Age bracket (*cases*)			
Infancy	0	0	1
Childhood	4	2	0
Adolescence – Adult	0	8	9
Combined AEDs			
Carbamazepine	3	5	5
Phenobarbital	0	1	1
Zonisamide	1	4	2
Clonazepam	0	0	1
Clobazam	1	4	2
Gabapentin	1	1	0
Topiramate	0	2	3
Lamotrigine	1	6	5

AED, antiepileptic drug.

The initial dosage of LEV was 10 mg/kg/day, and the dosage was increased by 10 mg/kg/day for 2 weeks. The maintenance dosage was 30–40 mg/kg/day; otherwise it could increase to 60 mg/kg/day if the effect of treatment was insufficient. However, the dosage was limited to 3000 mg/day.

2.2. Study design

The LEV blood concentrations were measured regularly during the treatment. The blood samples were obtained 1–2 h after LEV administration. In this study, the blood levels at 2 weeks and 1 and 2 years after reaching the maintenance dose were analyzed. The patients' blood was sampled at the pediatric outpatient clinic and measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) in the laboratory (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). A minimum sample of 0.1 mL of serum was frozen at -30 °C and saved. The efficacy of LEV was evaluated at the same times as the blood levels were analyzed. The seizure reduction rate at each evaluation was calculated as follows.

$$\text{Seizure reduction rate } (\%) = \frac{B - T}{B} \times 100$$

B: seizure frequency for 28 days before the start of LEV medication.

T: seizure frequency for 28 days before the evaluation.