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Effects of levetiracetam on seizure frequency and neuropsychological impairments in children with refractory epilepsy with secondary bilateral synchrony

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ABSTRACT

Purpose: In epilepsy with continuous spikes and waves during slow sleep (CSWS), which is a representative epileptic syndrome of secondary bilateral synchrony (SBS), the urgent suppression of this electroencephalographic (EEG) abnormality may be necessary to prevent the progression of neuropsychological impairments. The purpose of this study was to determine the efficacy of levetiracetam (LEV) on SBS, seizure frequency, and neuropsychological impairments in children with refractory epilepsy.

Methods: Eleven (seven male and four female) patients with refractory epilepsy with SBS on EEG, aged between 4.7 years and 11.3 years, were included in this study. After a 3-month baseline period, the patients were given LEV at an initial dose of 10 mg/kg/day for the first week, followed at increments of 5 mg/kg/day every week, up to 20 mg/kg/day. The LEV dose was then adjusted up to a maximum of 60 mg/kg/day, according to the clinician's judgment. EEG recordings and clinical evaluations were performed every 3 months, focusing on SBS. The occurrence of SBS was then scored, and the relationship between the score and the response to LEV treatment was evaluated. In comparison with the baseline SBS frequency, the EEG response to LEV treatment was classified, and responders were identified as having a $\geq$50% reduction in SBS frequency. In addition, in comparison with the baseline seizure frequency, response to LEV treatment was classified. Responders were identified as patients with complete cessation (100% seizure control) and a response of $\geq$50% reduction in seizures. Furthermore, neuropsychological impairments such as hyperactivity, impulsiveness, and inattention were evaluated before and after LEV treatment.

Results: Eight patients (72.7%) were considered responders. In addition, all eight patients were also considered responders for clinical seizures. Furthermore, 7 of 8 (87.5%) patients with response showed decreased hyperactivity and impulsivity after LEV administration.

Conclusions: The present data clearly indicate the usefulness of LEV in reducing both SBS on EEG and seizure frequency. LEV represents an important addition to the treatments available for refractory childhood epilepsies with SBS on EEG.

1. Introduction

Of the new antiepileptic drugs (AEDs), levetiracetam (LEV) has been approved as adjunctive treatment for new partial epilepsy in adults and children.[1–3] Studies published on the use of LEV in children with epilepsy have shown excellent pharmacokinetic and tolerability profiles, with few deleterious effects on cognitive function and no known pharmacokinetic interactions.[4] Furthermore, no teratogenic, mutagenic, or immunotoxic effects have been associated with administration of LEV in several animal species.[2]

For partial epilepsies, the relationships between seizures and interictal epileptiform discharges are controversial, but some interictal epileptiform activities have subtle clinical manifestations. LEV reduces the incidence of seizures[1] and interictal epileptiform discharges[5] in adult patients with localization-related epilepsy. However, little is known about these LEV efficacies for children with epilepsy.

Secondary bilateral synchrony (SBS) is the term given by Tukel and Jasper[6] to "bilaterally synchronous discharges which can be

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shown to arise from a unilateral cortical focus…" It has not yet been determined whether epilepsy with continuous spikes and waves during slow sleep (CSWS), which is a representative epileptic syndrome of SBS, is primary bilateral synchrony or SBS. Many of these children develop severe cognitive and behavioral deterioration that is unresponsive to medical treatment as the disease progresses.[7] In previous studies, seizures and the duration of paroxysmal anomalies appear to have been associated with prefrontal lobe growth abnormalities, which are associated with neuropsychological problems in CSWS.[8,9] These studies suggest that the urgent suppression of this electroencephalographic (EEG) abnormality may be necessary to prevent the progression of neuropsychological impairments. Accordingly, it is important to identify and use the best treatment options to remit seizures and EEG abnormalities as soon as possible to achieve the optimal prognosis in CSWS.[10]

The purpose of this study was to determine the efficacy of LEV on SBS, seizure frequency, and neuropsychological impairments in children with refractory epilepsy.

2. Methods

Eleven (seven male and four female) patients with refractory epilepsy with SBS on EEG, aged between 4.7 years and 11.3 years (mean, 7.5 years) at enrolment, were included in this study. The primary criterion for patient selection was the presence of frequent SBS on EEG recordings. In addition, the following criteria also had to be fulfilled: (1) between 1 and 18 years old; (2) seizures refractory to at least two first-line AEDs (appropriate AED for each seizure type or epileptic syndrome, with therapeutic concentrations of AEDs); (3) at least four seizures a month during the 3 months before LEV administration; (4) neuropsychological impairments such as hyperactivity, impulsivity, and inattention, as referred to in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[11]; and (5) at least 6 months of follow-up. Age at onset of epilepsy ranged from 3.1 years to 6.5 years (mean, 4.4 years). The mean duration of epilepsy history was 3.3 years (range, 1.6–4.8 years). All patients were affected by localization-related epilepsy or CSWS. In 10 patients, partial seizures evolved to secondary generalization. Participants in this study were taking a stable regimen of at most two or three concomitant AEDs, such as valproate sodium (VPA), zonisamide (ZNS), ethosuximide (ESM), and clobazam (CLB). However, children who were receiving carbamazepine (CBZ) at the time of first evaluation were excluded. The mean number of AEDs tried before introducing LEV treatment was 4.1 (range, 2–6).

After a 3-month baseline period, patients with epilepsy were given LEV at an initial dose of 10 mg/kg/day twice daily, which was increased to 15 mg/kg/day after 1 week, and then increased to 20 mg/kg/day after 1 week. During this period, LEV doses could be increased up to 60 mg/kg/day (or 3000 mg/day), according to the clinician's judgment. The goal of treatment in this protocol was to obtain seizure response ($\geq$50% seizure reduction) without adverse effects. The LEV dose was not increased in cases of complete seizure control and could be decreased in cases of adverse effects. The final dose regimen that was reached was maintained unchanged during the first 3 months of the evaluation period and could be adjusted for the following 3 months in cases of inadequate seizure control or adverse effects. The co-medication remained unchanged from baseline to the end of the 6-month evaluation period.

EEGs were performed on a 12- or 16-channel machine every 3 months. The duration of tracings was at least 20 min. For inclusion, it was necessary that at least one EEG be obtained without drug induction, showing a clear sequence of awake–drowsy–sleep–arousal–awake states. For this reason, parents were instructed to keep their children awake the night before the visit. Intermittent photic activation was done routinely, and hyperventilation was used when age permitted.

EEG studies were coded by number and read independently by two pediatric epileptologists or neurologists blinded to the identity of the patients. Agreement about the presence of SBS was required for inclusion of the patient in the study. According to a previous paper by Blume and Pillay[12] apparent SBS occurring exclusively during photic stimulation was not included. Recordings included sleep in the majority of patients.

EEG recordings and clinical evaluations were performed every 3 months, focusing on SBS. The occurrence of SBS during slow wave sleep on EEG with bipolar montage was scored, and the relationship between the score and the response to LEV treatment was evaluated. The spikes localized in only one hemisphere were not counted, since on EEGs with frequent SBS, such as CSWS, they were difficult to identify. The 3-month period before starting treatment was used as the baseline period for SBS frequency. SBS frequency on EEG was defined as the mean SBS frequency per minute. SBS frequency was compared in the same sleep stage in each patient. Six months later, the response to the dose increment for maintenance was assessed. In comparison with the baseline SBS frequency, the EEG response to LEV treatment was classified as follows:complete disappearance; response ($\geq$50% reduction in SBS frequency); no response ($<$50% reduction to $<$50% increase in SBS frequency); and exacerbation ($\geq$50% increase in SBS frequency). Responders were identified as patients with complete disappearance and response.

In addition, baseline seizure frequency, type, and duration were recorded by parents and caregivers over a period of 3 months before starting treatment with LEV. The numbers of seizures were recorded by parents and caregivers both at home and at day nursery/kindergarten/school. Seizure frequency, type, and duration, as well as adverse effects, were recorded in an epilepsy diary completed by parents and/or caregivers. Seizure frequency was defined as the mean seizure frequency per month. Six months after the dose increment for maintenance therapy, the response was assessed. In comparison with the baseline seizure frequency, response to LEV treatment was classified as follows: complete cessation (100% seizure control); response ($\geq$50% reduction in seizures); minimal response ($<$50% reduction in seizures); no response (no change in frequency); and exacerbation ($\geq$50% increase in seizure frequency). Seizure-free was defined as complete cessation for more than 3 months. Responders were identified as patients with complete cessation and response; they were followed-up for more than 6 months. Furthermore, neuropsychological impairments were evaluated before and after LEV treatment.

The significance of differences was evaluated by the *t*-test and the Bonferroni test; $P < 0.05$ was accepted as a significant result.

The study was carried out in accordance with the Declaration of Helsinki. Since LEV is not approved for children in Japan, informed consent was obtained from the parents of each patient following a full explanation of the procedures to be undertaken.

3. Results

The mean dose of LEV was 44.8 mg/kg/day (range, 19.4–57.7 mg/kg/day). The final mean dose was 1644 mg/day (450–2250 mg/day), using a b.i.d. dose schedule. Demographic data and baseline characteristics are summarized in Table 1.

Nine of eleven (81.8%) patients were considered responders for clinical seizures. In addition, 5 of 11 (46.4%) patients showed complete seizure cessation. Furthermore, all 5 frontal lobe epilepsy (FLE) patients showed seizure response.