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

Hideaki Kanemura [a,*], Fumikazu Sano [a], Kanji Sugita [a], Masao Aihara [b]

[a] Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Japan
[b] Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Japan

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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

* Corresponding author at: Department of Pediatrics, Faculty of Medicine, University of Yamanashi, 1110 Chuo, Yamanashi 409-3898, Japan.
Tel.: +81 55 273 9606; fax: +81 55 273 6745.
E-mail address: ykimu@yamanashi.ac.jp (H. Kanemura).

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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.

Table 1
Demographic data and baseline characteristics. M, male; F, female; CSWS, epilepsy with continuous spike and wave during slow sleep; FLE, frontal lobe epilepsy; ABPE, atypical benign partial epilepsy of childhood; TLE, temporal lobe epilepsy.

Case	Age (years)	Sex	Age of epilepsy onset (years)	Prior AED (*n*)	Epileptic syndrome
1	6.7	M	3.9	4	CSWS
2	7.1	M	4.1	5	FLE
3	4.7	F	3.1	3	FLE
4	5.6	F	3.4	4	FLE
5	9.2	M	6.5	4	ABPE
6	8.4	F	4.3	6	CSWS
7	6.2	M	4.1	3	FLE
8	7.6	M	4.2	4	ABPE
9	11.3	M	5.8	6	CSWS
10	4.9	F	3.2	2	FLE
11	10.3	M	6.1	4	TLE

All patients had sleep evaluated as part of their EEG. Eight patients (72.7%) were considered responders because they showed a reduction of $\geq$50% in SBS frequency on EEG. In addition, all 8 patients were considered responders for clinical seizures. Furthermore, 7 of 8 (87.5%) responder patients showed decreases in hyperactivity and impulsivity after LEV administration. Two of seven (28.6%) patients fulfilled the criteria for attention deficit/hyperactivity disorder of DSM-IV.[11] The efficacy for SBS on EEG was not apparent in one patient, but efficacy for clinical seizures was seen. In this patient (Case 3), efficacy for clinical seizures was achieved 2 months after LEV administration, but efficacy for SBS was not seen 9 months after LEV administration. Therefore, continuation of treatment for so long was justified in a child who responded clinically but did not respond on EEG. In the remaining two patients, there were no exacerbations. No efficacy for SBS or seizures was seen in two patients, but efficacy for emotional state was evident. Therefore, continuation of treatment for so long was justified in these children who did not respond. The efficacy of LEV for SBS on EEG and clinical seizures is summarized in Table 2. In 3 children (27.3%), there was a disappearance of SBS and paroxysmal abnormalities (Fig. 1). In 5 children (45.5%), there was a major decrease in SBS and paroxysmal abnormalities. In contrast, 6 children (54.5%) became seizure-free for the entire study 6 months after LEV administration, 3 (27.3%) showed a >50% reduction in seizure frequency for the entire 6 months, and 1 (9.1%) showed minimal response. In a further 1 patient (9.1%), seizure frequency remained unchanged, but no patients experienced an increase in seizure frequency. Serial data showed no change in patients showing responder status. Thus, tolerance to the anticonvulsant did not appear. Seizure reduction was demonstrated in the patients with atypical benign partial epilepsy of childhood (ABPE) and CSWS patients (Table 3). Both patients with ABPE showed complete disappearance of SBS and clinical seizures. Furthermore, 2 of 3 patients with CSWS showed complete disappearance of SBS and clinical seizures. On the other hand, 4 of 5 patients with frontal lobe epilepsy showed a major reduction of SBS. In contrast, no patients with temporal lobe epilepsy showed any reduction of SBS or clinical seizures (Table 3). Concomitant treatment was not modified during LEV administration.

Adverse events occurred in only 1 patient (9.1% of the total initial treatment group). The treatment-related adverse effect was drowsiness. This symptom was mild in this patient, and LEV discontinuation was not necessary. Hematological and biochemical tests were normal in all patients. None of the events causing hospitalization was considered by the investigators to be related to the study medication.

No clinically relevant, drug-related changes in clinical laboratory values, vital signs, physical examinations, neurological assessments, or electrocardiography were identified during the study.

4. Discussion

The results of this study indicate that LEV treatment may be effective in reducing EEG interictal abnormalities such as SBS in patients with refractory epilepsy. In addition, LEV treatment may be effective in reducing seizure frequency in localization-related epilepsies. Furthermore, the present data also suggest the usefulness of LEV in decreasing hyperactivity and impulsivity.

Freedom from SBS for 6 months was taken as the primary indicator of efficacy; disappearance of SBS was found in 50% of seizure-free patients. More than one-third of the present patients achieved freedom from SBS and epileptiform discharges over the entire study period for a mean of 9.4 months. The reduction in SBS was significantly related to the reduction in seizure frequency. All patients who achieved complete remission in SBS also showed an improvement in seizures. In a previous report, the reduction in epileptiform EEG abnormalities in juvenile myoclonic epilepsy was significantly related to the reduction in days with myoclonia.[13] In other reports, there were complete recoveries in 66.7% (2 of 3),[14] 50.0% (3 of 6),[15] and 55.0% (11 of 20)[16] of patients with drug-resistant CSWS after LEV treatment. Moreover, a reduction in EEG abnormalities and improvement in cognitive and behavioral functions were described with LEV in 9 cryptogenic and 3 symptomatic cases with CSWS.[4] The present results are consistent with these findings.

Table 2
The clinical efficacy of LEV for SBS on EEG and clinical seizures. SBS, secondary bilateral synchrony; LEV, levetiracetam; AED, anti-epileptic drug; HA, hyperactivity; IP, impulsivity; IA, inattention; VPA, valproate sodium; CLB, clobazam; ZNS, zonisamide; CBZ, carbamazepine; LTG, lamotrigine; ESM, ethosuximide; SLT, sulthiame.

Case	Frequency of SBS (times/min)		Seizure frequency (times/week)		Neuropsychological impairments		LEV dosage (mg/kg/day)	Present AED
	Pre	Post	Pre	Post	Pre	Post		
1	54	0	6	0	HA/IP (+)	HA/IP (−)	30.2	VPA + CLB + LEV
2	31	12	9	0	HA/IP (+)	HA/IP (−)	19.4	VPA + ZNS + LEV
3	28	25	6	1	HA (+)	HA (+)	35.5	CBZ + LTG + LEV
4	37	0	10	0	HA/IP (+)	HA/IP (−)	20.6	VPA + LEV
5	39	8	7	0	HA/IA (+)	HA/IA (−)	30.6	VPA + ESM + LEV
6	58	52	4	3	HA/IP (+)	HA/IP (+)	40.8	VPA + CLB + LEV
7	21	5	8	2	HA (+)	HA (−)	31.3	ZNS + LEV
8	33	9	4	0	HA (+)	HA (−)	40.1	VPA + SLT + LEV
9	61	0	7	0	HA/IP (+)	HA/IP (−)	57.7	VPA + CLB + LEV
10	27	7	6	1	HA (+)	HA (+)	24.2	ZNS + LEV
11	18	15	1	1	HA (+)	HA (+)	45.1	ZNS + LEV

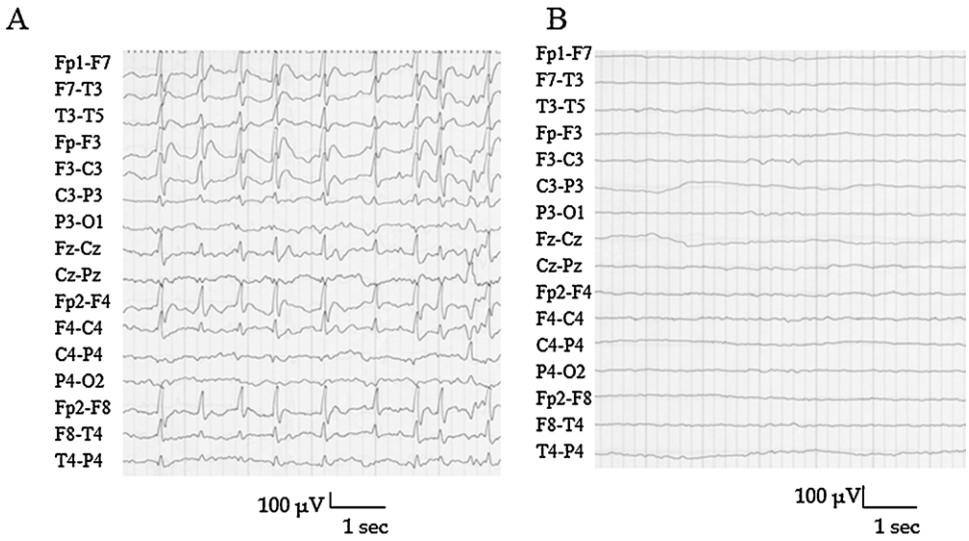

Fig. 1. EEG of patient 1 before (A) and after (B) introduction of LEV, recorded during sleep. EEG shows bilateral synchronous spike and slow-wave discharges (A). Six months after adding LEV, the EEG shows a great deal of improvement (B). The EEG shown is in bipolar montage, and the actual analysis was performed on bipolar montages for all EEGs.

A new broad-spectrum AED for childhood epilepsy should be effective in both partial and generalized seizures.[17] LEV, an add-on AED for partial-onset seizures in adults, shows good pharmacokinetics and tolerability in children, and it also demonstrates good efficacy in partial seizures and some generalized seizures.[18,19] Moreover, LEV is effective in treating children with specific epilepsy syndromes, such as CSWS, resulting in seizure reduction, improvement of alertness, and cessation of electrical status epilepticus during the sleep pattern on EEG.[20] In CSWS, the seizures demonstrate several types. In addition, the EEG pattern of CSWS consists of bilateral synchronous discharges. Focal spikes tend to be frontal. In our previous study, LEV appeared to demonstrate efficacy especially for frontal lobe epilepsy.[21] Thus, LEV may have a positive effect on SBS. The present results are in agreement with these findings.

In the present study, frontal lobe epilepsy, CSWS, and ABPE, which is associated with frontal lobe function,[22,23] achieved a higher benefit from LEV, whereas temporal lobe epilepsy had less benefit. Several studies found a relatively higher incidence of frontal foci as the likely principal triggers of bisynchronous discharges compared with control groups.[12,24] These findings appeared to contradict the conclusions of Tukel and Jasper that parasagittal lesions have a propensity to ignite bisynchronous discharges.[6] However, a relatively high incidence of frontal foci was also found by Niedermeyer in a similar study.[25] Another study reported that the frontal lobe was the most common origin of grand mal attacks.[26] Moreover, bisynchronous epileptiform discharges most commonly appear over the frontal lobes.[6,24,27] The reason why the frontal lobes serve as the most common triggers and principal sites of expression of SBS might be a significant regional variation in the capacity of the cortex to produce bilaterally synchronous discharges following establishment of bilaterally symmetrical epileptogenic foci.[28] Frontal foci easily elicited sustained bisynchronous discharges that often spread diffusely; temporal foci failed to produce bisynchronous discharges. The present results are in agreement with these findings. Thus, frontal epileptic origin seizures may obtain the greatest benefit from LEV. On the other hand, in previous studies, the thalamus appeared to play a crucial role as a pacemaker of rhythmic EEG activities such as SBS. In our previous report, interictal single photon emission computed tomography (SPECT) revealed thalamic hypoperfusion and ipsilateral cortical region involvement in children with epilepsy with SBS on EEG.[29] In another report, ictal SPECT showed positive findings of focal hyperperfusion in the frontal region and ipsilateral thalamus in frontal absence.[30] It was suspected that early thalamic injury was associated with CSWS.[31] These findings suggest that the thalamus may play a role in SBS on EEG. Therefore, epilepsies associated with the thalamo-cortical network may obtain greater benefit from LEV. However, the present sample was too small to draw this conclusion. In addition, although LEV demonstrated good efficacy in some children with CSWS, some findings suggested a high relapse rate in children.[4,20] Moreover, the 1 patient with temporal foci in the present study did not respond, but this number was too small to ascertain if this was similar to the effect seen in other studies. Further investigations are needed to clarify these points.

In contrast, it seems interesting that the frontal lobe epilepsies had a strong reduction in their SBS, but this did not correspond to seizure freedom, unlike the other epilepsy syndromes. In FLE, it is not uncommon that the inter-ictal EEG is normal despite frequent daily seizures. EEG findings may only correspond to clinical seizures in FLE, which may affect these findings. Further investigations are needed to clarify this point.

The final LEV doses that subjects received varied significantly. In our preliminary study, some patients showed improvements of EEG abnormalities without dose increase after seizure response. Accordingly, we gave the goal dose to each patient who obtained seizure response (≥50% seizure reduction) without adverse effects.

Table 3
Epilepsy syndromes and clinical efficacy of LEV. LEV, levetiracetam; SBS, secondary bilateral synchrony; ABPE, atypical benign partial epilepsy of childhood; FLE, frontal lobe epilepsy; TLE, temporal lobe epilepsy; CSWS, epilepsy with continuous spike and wave during slow sleep.

Epilepsy syndrome	Total (*n*)	Responder (≥50% reduction in SBS frequency)		Seizure free	
		n	%	*n*	%
ABPE	2	2	100	2	100
FLE	5	4	80	2	40
TLE	1	0	0	0	0
CSWS	3	2	66.7	2	66.7

One non-responder patient (case 6) developed an adverse effect (drowsiness). One patient (case 11) who showed no seizure response did not receive the maximal dose of LEV. However, in our preliminary study, all patients with seizure response showed a minimal response within the dose of 45 mg/kg/day of LEV. Accordingly, the variation in dose may potentially have a non-negligible effect on the results.

No correlation was found between the efficacy for SBS on EEG and LEV dosage. This finding contradicted the results by Boon et al.[32] However, LEV does not always decrease seizure frequency in a dose-dependent manner.[33] Further investigations will be needed to clarify these points.

In the present study, only one patient (9.1%) experienced adverse events without requiring LEV discontinuation. A relatively slow titration may result in this low incidence of adverse effects. LEV can be introduced rapidly, but a relatively slow titration of LEV may result in it being well-tolerated.

5. Conclusions

This add-on study shows that LEV is an alternative therapy in refractory childhood epilepsy syndromes. The present data clearly indicate the usefulness of LEV in reducing both SBS on EEG and seizure frequency. Frontal epileptic origin seizures may obtain the greatest benefit from LEV. Since treatment options for refractory epilepsies are limited, LEV represents an important addition to the treatments available for refractory childhood epilepsies with SBS on EEG.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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