Journal of Clinical Neuroscience 19 (2012) 956–960

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

The acute effects of levetiracetam on nocturnal sleep and daytime sleepiness in patients with partial epilepsy

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ARTICLE INFO

Article history:
Received 27 June 2011
Accepted 30 September 2011

Keywords:
Daytime sleepiness
Epilepsy
Levetiracetam
Polysomnography
Sleep

ABSTRACT

This study investigated the effect of the novel antiepileptic drug levetiracetam (LEV) on sleep in eleven patients with partial epilepsy. At baseline and one week after therapy with LEV (1000 mg/day), patients underwent polysomnography (PSG) and the Multiple Sleep Latency Test (MSLT). Patients also rated their own degree of sleep disturbance and daytime sleepiness with the Athens Insomnia Scale (AIS) and the Epworth Sleepiness Scale (ESS). A group of 10 age- and gender-matched control participants were also included in the study. Patients had decreased total sleep time and increased daytime sleepiness compared to baseline, as evaluated by AIS subscales. Furthermore, LEV therapy significantly decreased the rapid eye movement sleep time and percentage as measured by PSG. Patients reported a significant increase in ESS score but did not exhibit changes in MSLT performance after LEV treatment. The study demonstrated that short-course LEV treatment can affect subjective sleep time and objective sleep architecture. Furthermore, LEV treatment affected subjective daytime sleepiness but did not influence objective mean daytime sleep latencies in patients with partial epilepsy.

1. Introduction

Patients with epilepsy report greater levels of sleep disturbance than people without epilepsy.[1] There are several possible causes of sleep disturbance in this group of patients, including coexisting sleep disorders, effects of seizures, and the effects of anticonvulsant drugs.[2] Sleep, epilepsy, and the effects of antiepileptic drugs (AED) are closely related and are a common concern for patients.[1] Sleep is a powerful modulator of epileptic activity. Significant sleep disturbance in patients with epilepsy has been associated with impaired quality of life and impaired seizure control. In turn, epileptic activity can alter the sleep–wake cycle and sleep architecture.[3] AED play a key role in the mutual interactions between sleep and epilepsy.[3,4] These drugs have varied effects on sleep structure, which can be beneficial or detrimental.[2] The most common side effects of AED include alterations in sleep architecture and variation in the degree of daytime sleepiness.[5] Severe daytime somnolence affects activities and cognitive function, which may result in patients terminating treatment due to an inability to tolerate the side effects of the drugs. It is therefore important to examine the effects of AED on sleep.

Findings on AED effects are inconsistent because of differences among studies, including variations in study populations, drug dose and timing, duration of treatment, failure to control for seizures, and concomitant AED.[6] Furthermore, it is unethical to evaluate the effects of long-term AED treatment in people without epilepsy, and it is dangerous to discontinue previous AED treatment in patients with epilepsy.[3] The duration of treatment with AED is an important factor in study outcomes. Studies have confirmed that many AED have distinct acute and chronic effects on sleep.[7–10] In studies of the effects of phenytoin on sleep structure, significant differences were found between short-term and long-term effects. Acute effects were characterised by decreases in sleep onset latency, Stage 1 (S1), and Stage 2 (S2), whereas an increase was observed in slow-wave sleep (SWS), and rapid eye movement (REM) sleep was unchanged. Conversely, long-term effects were an increase in S1 and S2 and a decrease in SWS, with no change in REM sleep.[7,8]

Levetiracetam (LEV) is a novel AED that is effective for the treatment of partial seizures as mono- or polytherapy. Bazil at al. reported that LEV did not have major effects on sleep structure in healthy volunteers after 28 days of treatment.[11] Another study showed that after three weeks of treatment LEV increased total sleep time, sleep efficiency, and decreased waking after sleep onset in healthy adults. There were no changes in the Epworth Sleepiness Scale (ESS) or the Multiple Sleep Latency Test (MSLT).[12] A recent report showed an increase in sleep efficiency in patients with epilepsy after 4–6 weeks of treatment with LEV.[13] These studies suggest that LEV does not have detrimental effects on sleep; rather, LEV consolidates sleep and may be a sleep-friendly AED.

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http://dx.doi.org/10.1016/j.jocn.2011.09.032

These results are not consistent with clinical observations after LEV treatment. Patients with epilepsy who take this medication occasionally report sleep disorders that affect their work and study. LEV has been reported to cause daytime sleepiness in 4–15% of patients; as a result, 10% of patients discontinued treatment.[14] The purpose of this study was to evaluate the acute effects of LEV treatment on nocturnal sleep and daytime somnolence in adult patients with partial epilepsy. The study used polysomnography (PSG), the MSLT, and subjective sleep questionnaires, to examine the subjective and objective effects on sleep in patients with partial epilepsy who were treated with LEV for one week.

2. Materials and methods

2.1. Patients

Patients in the Outpatient Neurology Clinic at the West China Hospital of Sichuan University were enrolled. The study was approved by the hospital Ethics Committee, and written informed consent was obtained from all patients before screening. Patients were initially screened by a neurologist. Eleven patients with partial epilepsy (simple partial, complex partial, or partial seizure with secondary generalisation) were selected for the study. Patients who received monotherapy with carbamazepine, valproate, or lamotrigine before the study were required to be at a stable dose for at least one month.

Patients were free of sleep disorders according to their clinical history. Patients with PSG-confirmed sleep apnoea and periodic leg movement syndrome were excluded from the study. Other exclusion criteria included: clinically relevant medical or psychiatric disorders, intake of drugs with known effects on sleep (except AED), and women who were pregnant or breastfeeding. Patients were seizure-free and not sleep-deprived for $\geqslant$24 hours before and during the examination. A group of 10 age- and gender-matched healthy volunteers served as controls (five female, five male; mean age = 33.60 ± 13.07 years, range = 20–65; $p = 0.852$).

2.2. Study design

The study was observational in design. Patients underwent study sessions on two separate occasions (at baseline, and one week after therapy with LEV), whereas control participants were assessed only once (at baseline). Patients were given LEV at a dose of 500 mg twice daily for one week. A 1000 mg dose was chosen for the study because it is the mean recommended dose in clinical practice. Doses of other AED were not changed during the study period.

2.3. Questionnaire evaluations

Sleep questionnaires were completed by the patients at baseline and at the end of the one-week treatment period, whereas control participants completed the assessment only at baseline. The Athens Insomnia Scale (AIS), a self-assessed psychometric instrument, was used to assess sleep difficulty. The questionnaire consists of eight items: the first five relate to sleep induction, awakening during the night, early morning awakening, total sleep time, and sleep quality, and the last three items pertain to well-being, functioning capacity, and sleepiness during the day. Each item is rated from zero to three, and the total score ranges from zero (absence of any sleep-related problem) to 24 (the most severe degree of insomnia). Participants were instructed to answer positively if they had experienced the sleep difficulty described in each item at least three times a week during the past week.[15]

The Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness. Each participant completed the Chinese version of the ESS,[16] an eight-item test for assessing daytime sleep propensity in different hypothetical situations during the preceding week. Each item is rated from zero to three, and the total score ranges from zero to 24. An ESS score $\geqslant$10 indicates excessive daytime somnolence (EDS).[17]

2.4. PSG evaluations

All participants underwent PSG evaluation at baseline. Overnight PSG consisted of continuous recordings from six electroencephalographic (EEG) leads (F4-M1, C4-M1, O2-M1, F3-M2, C3-M2, O1-M2), two electro-oculographic leads (ROC-M1, LOC-M2), an electrocardiogram and a submental and anterior tibialis electromyogram. Other parameters measured included nasal and oral airflow, respiratory effort (thoracic and abdominal), oxygen saturation, body position, and snoring. Sleep analysis was performed according to the international criteria of the American Academy of Sleep Medicine.[18] Polysomnograms were scored by a senior technician who was blinded to all participants.

The following sleep variables were measured: total sleep time, sleep latency, sleep efficiency, time and percentage spent in non-REM one, two, three and REM sleep stages, REM sleep latency, wake time after sleep onset, number of awakenings (>15 s), number of arousals (>3 s to $\leqslant$15 s), apnea–hypopnea index (AHI), and periodic leg movement index (PLMI). After a week of stable LEV treatment, all patients underwent the second monitoring session.

2.5. MSLT

The MSLT is an objective method for evaluating daytime sleepiness that comprises four, 20 min nap trials at intervals of two hours. The MSLT sessions took place at 9 am, 11 am, 1 pm, and 3 pm. Daytime sleep propensity was calculated for each participant as the average of the four naps (mean daily sleep latency). All participants underwent the MSLT on the second day after overnight PSG, and the patients underwent the evaluation again after treatment.

2.6. Statistical analysis

Statistics were calculated using the Statistical Package for the Social Sciences version 17.0 (SPSS, Chicago, IL, USA). All statistical tests were two-tailed, and significance was set at $p < 0.05$. Baseline AIS and ESS scores, and sleep parameters of PSG and the MSLT, were compared in patients with epilepsy who were drug-free, and in control participants, by the Mann–Whitney U-test. In patients with epilepsy, differences between variables before and after treatment were analysed by the non-parametric Wilcoxon paired test.

3. Results

3.1. Patient demographics and clinical characteristics

Ten patients completed the one-week study period and received continued therapy with LEV (1000 mg/day) (Table 1). One patient discontinued with the study because of a seizure during PSG. On the basis of clinical, neuroradiological, and EEG characteristics, nine patients were diagnosed with partial cryptogenic epilepsy, and one patient was diagnosed with partial symptomatic epilepsy. Four patients had not received any AED therapy before the study, and the other six patients were required to be