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Brief Communication

Effects of levetiracetam on sleep in normal volunteers

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Abstract

Background. Epilepsy patients commonly suffer from sleep disturbances, and these can exacerbate memory dysfunction and seizures. Sleep can be affected by seizures, independent sleep disorders, or anticonvulsant drugs. Levetiracetam is a novel anticonvulsant effective for the treatment of partial seizures. We studied the effects of levetiracetam (LEV) on sleep using polysomnography in normal subjects.

Methods. Subjects (aged 18–40) were screened for freedom from sleep disorders, excessive daytime sleepiness, and depression. Screening overnight polysomnography was performed, followed by baseline polysomnography. Subjects were randomized to placebo or LEV, titrated to 1000 mg twice daily over 9 days. Polysomnography was repeated on Treatment Day 28. Differences between baseline and treatment in the drug and placebo groups were compared using single-factor ANOVA.

Results. Seventeen subjects were enrolled; 14 completed the study (8 placebo, 6 LEV). All subjects who remained on LEV were able to tolerate the target dose. There were no significant differences between the placebo and drug groups with respect to baseline sleep characteristics. When baseline polysomnography was compared with treatment polysomnography, there were no differences in the change in sleep efficiency, sleep latency, total sleep time, REM latency, or percentages of REM, stage 1, stage 2, or slow wave sleep. There was an increase in the number of awakenings in the drug group that was significant compared with placebo.

Conclusion. These results suggest that LEV does not have major effects on sleep structure.

Keywords: Sleep; Polysomnography; Anticonvulsant drugs; Levetiracetam

1. Introduction

Sleep disturbance and daytime drowsiness are common in epilepsy patients [1–3]. Although our society tends to accept poor sleep as the norm, it can result in considerable impairment of daytime functioning, even in normal individuals. In patients with epilepsy, the consequences are potentially more severe. Inadequate sleep can exacerbate the drowsiness and memory dysfunction common to these individuals, and can contribute to intractable seizures [4]. Even more concerning is the potential for a cycle of sleep disruption, worsening seizures, and further impairment of sleep, which can be responsible for the intractability of epilepsy in some patients.

Potential causes of sleep disturbance include inadequate sleep hygiene, coexisting sleep disorders, and circadian rhythm disturbances [1,2]. Seizures themselves can disrupt sleep, and even daytime seizures have been shown to disrupt the following night's sleep [5]. Anticonvulsant drugs and the vagus nerve stimulation can also alter sleep, in both positive and negative ways, and these effects are independent of their anticonvulsant actions [6–8]. Although there are several studies of older anticonvulsants, relatively little is known about the effects of the newest anticonvulsant drugs on sleep [9].

Levetiracetam is an anticonvulsant drug effective for the treatment of partial seizures. Sleep complaints are not listed among the common side effects [8]. We studied the effects of levetiracetam on sleep using normal subjects to

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isolate the effects of the drug itself from its effects on seizures.

2. Methods

Normal subjects between the ages of 18 and 40 were recruited from the community. Informed consent was obtained before any study-related assessments were performed. Because numerous anticonvulsants have been shown to affect the percentage of REM sleep [10–17] this was chosen as the primary outcome variable. On the basis of previous studies in patients with epilepsy [10], we estimated that it was necessary to assign at least five subjects to each treatment arm to detect a difference in REM sleep percentage; a total of 16 were targeted (8 per treatment group) to allow for dropouts. Secondary outcome variables included percentages of stage 1, stage 2, and slow wave sleep; sleep efficiency; and numbers of arousals and awakenings. With the use of numbers similar to those in the above study, effects on stage 1 sleep (with phenytoin and valproate) and slow wave sleep (with gabapentin) were seen; therefore, changes in at least some secondary variables, if similar in magnitude to changes caused by other AEDs, could be expected with this sample size. Subjects were initially screened by a neurologist by structured interview to ensure that they were free of sleep disorders and not taking any medication except occasional nonsteroidal anti-inflammatory agents or oral contraceptives. Subjects also were screened for excessive daytime sleepiness with the Epworth sleepiness scale, and for depression using the Beck Depression Inventory. Women of childbearing potential could not be pregnant when entering the trial, and were instructed in the use of adequate birth control (oral contraceptive or barrier) throughout the trial. Urine pregnancy tests were administered prior to treatment with drug or placebo. No caffeine was allowed after noon on days of polysomnography.

Subjects without signs of sleep disorder, significant daytime sleepiness, or depression and who signed an informed consent were scheduled for screening overnight polysomnography in the laboratory. So long as no significant sleep disorder was seen, the subjects were randomized to drug or placebo, and the following night, a baseline study was performed for comparison to treatment arms of the study. Subjects were then given levetiracetam (LEV) or placebo, initially at a dose of 250 mg twice daily, increasing to 500 mg twice daily after 3 days if tolerated, then 750 mg twice daily after 3 more days, then 1000 mg twice daily after 3 more days (total of 9 days of titration). Subjects were contacted weekly during the treatment, but instructed to call immediately if they experienced side effects. If the side effects were unacceptable, the titration rate could be slowed; however, the subject remained in the study so long as he or she could tolerate at least 500 mg twice daily by 5 days prior to the next polysomnogram. The daily dose of 2000 mg was chosen because it represents the median recommended dose and the median dose in the pivotal trials [11]. Polysomnography was repeated on Day 28 of treatment or placebo. Sleep latency, total sleep time, sleep efficiency, and time in each sleep stage (as a percentage of total sleep time) were calculated. Awakenings were defined as at least one epoch scored as awake after a sleep period; arousals were defined as a shift to higher EEG frequencies during a sleep epoch without progression to full wakefulness, according to the criteria of the American Sleep Disorders Association [12]. Differences between baseline and treatment were calculated, and drug was compared with placebo using single-factor ANOVA. Polysomnograms were all scored by the same blinded investigator.

Blood was taken for measurement of serum LEV to verify compliance.

3. Results

A total of 17 subjects met the aforementioned criteria and were enrolled in the study. One subject (randomized to LEV) dropped out after three doses of study medication due to agitation; another subject dropped out due to unrelated illness after randomization but before the second polysomnogram. A third subject (randomized to LEV) had inadequate polysomnography due to technical failure. This left 14 subjects available for evaluation. Eight had been randomized to placebo, and six to LEV. All subjects who remained on LEV were able to tolerate the target dose of 2000 mg/day, and were tested while taking this dose. The characteristics of the subjects are summarized in Table 1.

All subjects taking drug had measurable LEV levels (range, 11–42; mean $\pm$ SD, 24 ± 5). Results are outlined in Table 2. There were no significant differences between those taking placebo and drug with respect to baseline sleep characteristics. When baseline polysomnography was compared with treatment polysomnography, there were no differences in the change in sleep efficiency, sleep latency, REM latency, total sleep time, or percentages of REM, stage 1, stage 2, or slow wave sleep. There was an increase in the number of awakenings (defined as a period of at least one epoch of wakefulness after sleep onset) in the drug group that was significant compared with placebo ($P < 0.05$). Arousals were also increased; however, this did not reach statistical significance.

4. Discussion

These results suggest that LEV does not have major effects on sleep structure. There was, however, a significant increase in the number of awakenings in subjects taking LEV; this is of questionable clinical significance as awakenings were brief and there was no overall difference in sleep efficiency. The clinical significance of increased awakenings could be further assessed by direct measurement of drowsiness using subjective (Epworth sleepiness scales) or objective (multiple sleep latency testing) tests in patients chronically treated with LEV. This study enrolled a relatively small number of subjects; it could be that more subtle changes in sleep (less than seen with other agents) would

Table 1
Characteristics of patients

	Mean age (range)	% Female	Mean baseline sleep time (min)	Mean baseline Epworth score	Mean LEV
Drug ($n = 6$)	32 (25–40)	83	370.25	4.3	24.01
Placebo ($n = 8$)	30 (22–37)	25	406.81	6.8	0

Table 2
Results of polysomnography

	Stage 1 (%)	Stage 2 (%)	SWS[a](%)	REM %	REM latency (min)	TST (min)	SE (%)	No. of arousals	No. of awakenings
Baseline									
Drug	11.4 (± .9)	52.8 (± 2.0)	16.2 (± 2.5)	19.6 (± 1.2)	98.27 (± 18.9)	370.25 (± 13.32)	90.1 (±2.6)	36 (± 10.9)	10 (± 1.3)
Placebo	8.1 (± 1.4)	57.6 (± 2.0)	16.1 (± 1.7)	18.2 (± 1.1)	87.63 (± 6.18)	406.81 (± 10.82)	94.6 (± 1.4)	37.5 (± 4.9)	12 (± 2.5)
Treatment									
Drug	16.3 (± 3.4)	52.8 (± 4.1)	14.4 (± 2.0)	16.5 (± 2.2)	144.92 (± 25.3)	358.67 (± 23.25)	88 (± 3.9)	60 (± 22.9)	17[b] (± 1.6)
Placebo	7.7 (± 1.9)	60.1 (±2.0)	16.8 (±2.8)	15.4 (±2.0)	112.81 (±21.1)	376.69 (± 10.04)	95.1 (± 1.3)	34 (± 7.2)	8 (± 1.8)

[a] SWS, slow wave sleep; TST, total sleep time; SE, sleep efficiency.
[b] $P < 0.05$ for drug versus placebo, baseline—treatment.

become evident in a larger group. These results differ somewhat from those of another study, in which single-dose LEV was studied as monotherapy in normal volunteers and as add-on (to carbamazepine) therapy in subjects with epilepsy [13]. These authors found no effect on sleep efficiency or amount of slow wave or REM sleep in either group; they saw no difference in the number of awakenings but did find increased REM latency and stage 2 sleep. Our study used a higher dose (2000 mg/day, compared with 1000 mg for the Bell study) and a longer treatment period (28 days compared with a single dose); this could be partly responsible for the observed differences.

Research suggests that other anticonvulsant drugs have more pronounced effects on sleep. Benzodiazepines and barbiturates, although used less commonly for chronic treatment of seizure disorders, are associated with the most convincing evidence for detrimental effects on sleep. While both classes of medications reduce sleep latency, they also decrease the amount of REM sleep [14,15]. Phenytoin increases light sleep, decreases sleep efficiency, and decreases REM sleep [10,14–18]. Findings for carbamazepine are more variable, but there also seems to be a reduction in REM sleep [17], particularly with acute treatment [19,20].

Studies of newer agents suggest fewer detrimental effects on sleep. Lamotrigine was shown to have no effect on sleep in one study [19], but another demonstrated decreases in slow wave sleep [21]. Gabapentin has no detrimental effects on sleep and, in fact, seems to enhance slow wave sleep in subjects with epilepsy [10,19] and in normal volunteers [22,23]. Effects of zonisamide and oxcarbazepine on sleep and sleep disorders are not known; a study of topiramate in subjects with new-onset epilepsy indicated no effect on daytime vigilance [24]; however, effects on sleep structure were not tested. Subjects taking anticonvulsants known to disrupt sleep (phenobarbital, phenytoin, carbamazepine, or valproic acid) experience increased daytime drowsiness compared with subjects with epilepsy who are not taking anticonvulsants [25].

5. Conclusion

This study, although small, suggests that levetiracetam appears to have no clinically significant effects on sleep structure. The results are consistent with the clinical impression that most subjects taking this medication do not commonly complain of drowsiness or sleep problems. A larger study is needed to determine the possibility of more subtle changes associated with this medication.

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