Dose-Response Effects of Tiagabine on the Sleep of Older Adults

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Study Objectives: To evaluate the dose- response effects of tiagabine on sleep and safety measures in healthy older adults.

Design: Randomized, double-blind, Latin-square design.

Setting: Sleep laboratory.

Participants: Twenty-four healthy older adults (11 men, 13 women; mean age 68.0 ± 6.2 years)

Interventions: Tiagabine 2, 4, or 8 mg, or placebo, each given on two consecutive nights.

Measurements and Results: Polysomnography revealed that compared with placebo, tiagabine 4 mg increased total sleep time, reduced wake after sleep onset, and increased minutes of slow-wave sleep. Tiagabine 8 mg decreased wake after sleep onset, increased slow-wave sleep, and improved a sleep-continuity index. No differences were seen between the 2-mg dose and placebo. Subjective ratings indicated fewer awakenings with the 8-mg dose. Central nervous system adverse events were somewhat higher in the 8-mg condition only. Measures of morning performance were minimally affected.

Conclusions: Research with tiagabine at dosages of 8 mg or less appears warranted in elderly clinical populations.

Key words: Tiagabine, elderly, slow-wave sleep, sleep maintenance, wake after sleep onset, dose response

Citation: Walsh JK; Randazzo AC; Frankowski S et al. Dose response effects of tiagabine on the sleep of older adults. SLEEP 2005;28(6):673-676.

INTRODUCTION

TIAGABINE, A SELECTIVE γ-AMINOBUTYRIC ACID REUPTAKE INHIBITOR, HAS BEEN REPORTED TO HAVE SLEEP-ENHANCING EFFECTS. Slow-wave sleep (SWS) in rodents is increased by tiagabine.1 In a study of healthy elderly subjects, tiagabine 5 mg significantly increased SWS and improved sleep efficiency by reducing wakefulness during the sleep period.2 These findings were intriguing because the elderly have reduced SWS and reduced sleep efficiency. Recently, subjective improvements in sleep have been reported with open-label use of tiagabine in patients with posttraumatic stress disorder1 and generalized anxiety disorder.2

Unlike currently available sleep-promoting medications, tiagabine does not act as an agonist at the benzodiazepine receptor. Rather, it produces an increase in extracellular γ-aminobutyric acid by inhibiting reuptake on the GAT-1 transporter.3 Tiagabine has no direct effect on γ-aminobutyric acid receptors or on other neurotransmitters or receptors.4 The distinct mechanism of action, relative to benzodiazepine receptors, may relate to the differing effects on sleep architecture. In contrast to the SWS-promoting property of tiagabine, benzodiazepine receptors have been reported to decrease SWS and slow-wave activity. Absorption of tiagabine is rapid, with a tmax of about 45 minutes in the fasting state and an elimination half-life of 7 to 9 hours in heptatically noninjured patients. The primary metabolic pathway for tiagabine is CYP3A4, and the P450 system is neither induced nor inhibited. In the United States, tiagabine is approved as adjunctive therapy for partial seizures, with the dose to be titrated starting at 4 mg per day.

To further pursue the possibility that tiagabine may be helpful for individuals with sleep disruption, especially older adults, clarification of an appropriate dose range is needed. The effect of 3 doses of tiagabine on the sleep of elderly subjects without sleep complaints was assessed in this study. Additionally, safety and tolerability of the 3 doses was evaluated. We chose to study healthy elderly individuals to reduce safety concerns until more is known about various doses of tiagabine used to promote sleep in older persons. Further, healthy elderly have reduced SWS and more sleep fragmentation relative to younger adults, and those dimensions of sleep appear to be appropriate targets for tiagabine.

Measurements and Results: Polysomnography revealed that compared with placebo, tiagabine 4 mg increased total sleep time, reduced wake after sleep onset, and increased minutes of slow-wave sleep. Tiagabine 8 mg decreased wake after sleep onset, increased slow-wave sleep, and improved a sleep-continuity index. No differences were seen between the 2-mg dose and placebo. Subjective ratings indicated fewer awakenings with the 8-mg dose. Central nervous system adverse events were somewhat higher in the 8-mg condition only. Measures of morning performance were minimally affected.

Conclusions: Research with tiagabine at dosages of 8 mg or less appears warranted in elderly clinical populations.

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METHODS

This study was conducted in accordance with the Declaration of Helsinki at 2 sites after approval by both institutions’ human research committees. A double-blind, placebo-controlled, Latin-square design was used to investigate 2, 4, and 8 mg of tiagabine (T2, T4, T8, respectively) versus placebo.

Subject Selection, Screening and Adaptation

Media advertisements were used to recruit healthy men and women between 60 and 80 years of age (inclusive). An initial telephone interview screened individuals for known unstable medical conditions, psychiatric illness, prohibited medications, sleep complaints, habitual morning rise time outside of the 5:00 AM to 9:00 AM window, and excessive alcohol or caffeine consumption. Prohibited medications included all psychotropic drugs. Stable doses of other necessary medication were allowed provided they were continued throughout the entire study.

Twenty-six subjects (13 men, 13 women) with a mean age of 67.8 ± 6.1 years without complaints about their sleep provided written informed consent after a complete description of the study procedures. Medical, sleep, and psychiatric histories, physical examination, urine drug screen, and routine blood chemistry and procedures. Medical, sleep, and psychiatric histories, physical examination, urine drug screen, and routine blood chemistry and urinalysis ensured that all subjects were free of unstable medical conditions, psychiatric disorders, kept a regular sleep schedule, habitually consumed < 10 alcoholic drinks per week and < 400 mg caffeine per day, and did not take central nervous system active medications. One night of polysomnography (PSG) was conducted after single-blind administration of placebo to screen for sleep apnea (apnea-hypopnea index > 10) and periodic limb movements (periodic limb movements arousal index > 15) during sleep, as well as to adapt subjects to the laboratory procedures and environment. The following morning, subjects practiced the psychomotor and memory test and became familiar with subjective rating forms.

Procedures

Tiagabine 2 mg, 4 mg, 8 mg (in 2-mg tablets) or matching placebo, was administered 30 minutes before bedtime on each of 2 consecutive nights. Four pills were administered each night; four 2-mg tablets for the 8-mg condition, three 2-mg tablets and 1 placebo tablet for the 6-mg condition, and so on, to maintain blinding of both subjects and study staff. Two-night treatment periods were separated by 5 nights at home without study medication. Subjects arrived at the study site approximately 1.5 hours before their habitual bedtime for each PSG, and bedtime was held constant for all PSG nights. Standard PSG techniques were used, and scoring was performed at 1 site, according to standard criteria. PSG recording time was 480 minutes on all nights. For nights on which subjects slept at home, they were instructed to retire at their habitual bedtime ± 30 minutes.

Morning procedures included a postsleep questionnaire to collect subject-reported estimates of sleep, Digit Symbol Substitution Test, Karolinska Sleepiness Scale, and Immediate and Delayed Recall Word Test. All were completed about 10 to 20 minutes after morning wake-up time, except for the delayed recall which occurred 30 minutes after completion of immediate recall. Patient-reported adverse events and vital signs were documented at each study visit. A final safety evaluation, including a physical examination, was performed 3 to 7 days after completing the final PSG.

Statistical Analyses

Because the primary purpose of the study was to identify a dose to be tested in clinical populations, statistical comparisons of interest involved each tiagabine dose versus placebo. PSG, subject-reported sleep variables, and morning assessments were analyzed with an analysis of variance model with terms for study site, period, night, and treatment. After averaging the 2 measurements (nights 1 and 2) of each variable for each condition, paired comparisons between each dose, and placebo were made with an analysis of variance using the mean square error from the above model. All tests were 2-tailed, and α was 0.05. All statistical comparisons reported below include data for 24 subjects with the exception of latency to SWS, which included data for 22 subjects. The 2 subjects were excluded because both had less than 3 minutes of SWS in all conditions.

RESULTS

Twenty-four (11 men, 13 women; mean age 68.0 ± 6.2 years) of 26 subjects completed the study. One subject was terminated...
because of noncompliance and another because of unsteady gait the morning following the first dose of 8 mg.

**PSG Variables**

PSG data for each tiagabine dose and placebo are presented in Table 1. T2 did not differ significantly from placebo on any variable. T4 had a significantly greater mean TST (407.7 minutes) than placebo (396.0 minutes; \( P = .022 \)) and significantly less WASO (64.9 minutes) compared with placebo (77.2 minutes; \( P = .019 \)). Minutes of SWS increased for T4 (59.7) relative to placebo (44.5; \( P = .015 \)). Latency to SWS for T4 was shorter than for placebo, although not significantly (38.2 vs 51.0 minutes, \( P = .129 \)). There also was a trend for less stage 1 sleep with T4 (73.9 minutes) compared with placebo (81.3 minutes; \( P = .059 \)).

T8 showed a trend toward increased TST (\( P = .073 \)) but no difference for WASO. Rapid eye movement (REM) sleep latency was longer for T8 (94.2 minutes) than placebo (71.8 minutes; \( P = .001 \)). Compared with placebo, T8 also showed significantly more SWS (87.0 vs 44.5 minutes; \( P < .0001 \)), less stage 1 sleep (62.4 vs 81.3 minutes; \( P < .0001 \)) and less REM sleep (58.4 vs 68.3 minutes; \( P = .01 \)). Latency to SWS was reduced with T8 relative to placebo (33.1 vs 51.0 minutes, \( P = .01 \)).

The ratio of stage 3+4/(stage 1 + WASO) has previously been reported as a potential measure of sleep fragmentation.\(^9\) There was a significant difference between this ratio for T8 as compared with placebo (1.03 ± 1.27 vs 0.37 ± 0.37; \( P < .0002 \)), reflecting reduced fragmentation with T8. Ratios for T2 and T4 (0.41 and 0.56, respectively) did not differ from placebo. Figure 1 shows the dose response for this measure of sleep fragmentation.

**Postsleep Questionnaire**

On the postsleep questionnaire, subjects provided self-reports for length of sleep, time to fall asleep, time awake after falling asleep, number of awakenings, and quality of sleep. Only reported mean number of awakenings for the T8 condition (3.70 ± 3.44) differed from placebo (2.65 ± 3.44; \( P < .032 \)). All other self-reported sleep variables for any tiagabine dose did not differ from placebo.

*Figure 1—The mean ratio of stage 3 + stage 4 sleep in minutes/(stage 1 sleep + wake after sleep onset [WASO] in minutes) for each treatment condition. \( P < .0002 \) vs placebo.*

**Measures of Morning Sedation and Memory**

The Karolinska Sleepiness Scale, Digit Symbol Substitution Test, and ratings of level of alertness and ability to concentrate showed no differences among conditions. Similarly no differences were seen on immediate word recall. The mean delayed recall score was slightly, but significantly, lower in the T8 condition relative to placebo (8.75 ± 3.79 vs 9.80 ± 3.37; \( P < .036 \)).

**Adverse Events**

The rate of adverse events did not differ among conditions, except for those related to the central nervous system. Eight subjects reported 13 adverse events dealing with the central nervous system during the T8 condition, as compared with 3 (3 adverse events), 2 (2 adverse events), and 2 (5 adverse events) subjects in the placebo, T2, and T4 conditions, respectively. Table 2 contains central nervous system adverse-event data for the 26 subjects who received at least 1 dose of study medication. None of the adverse events was judged by a study physician to be serious. One subject was discontinued because of unsteady gait the morning following the first PSG during the T8 condition. The subject’s gait returned to normal within 1 hour without intervention.

**CONCLUSIONS**

This exploratory study in healthy older adults suggests that tiagabine 4 and 8 mg have positive effects on sleep, particularly those variables related to improved continuity and maintenance of sleep. An increase in the ratio stage 3+4 sleep/(stage 1 sleep + WASO) reflects the combined effects of tiagabine on stages 3+4 sleep and on stage 1 sleep and wake. The reduction in WASO and stage 1 sleep may result from reduced arousability mediated by more time spent in SWS. Although the absolute change in minutes of WASO was seemingly small in this study, our subjects had no complaints about their sleep, and the observed amount of WASO is similar to that of other studies of healthy elderly persons.\(^{10}\) More-significant effects on WASO may be seen in elderly individuals with sleep-maintenance difficulty and higher WASO values. Additionally, lowering PSG WASO with a hypnotic has not been described frequently, perhaps because of the mandated 8 hours in bed for the vast majority of PSG trials. For example, WASO is generally not reduced with short-acting hypnotics, nor with a low dose of a hypnotic with an intermediate duration of

**Table 2—Adverse Events Associated With the Central Nervous System for Each Study Drug Condition**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Tiagabine 2 mg</th>
<th>Tiagabine 4 mg</th>
<th>Tiagabine 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>All central nervous system adverse events</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>5 (2)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unsteady gait</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Weakness</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tiredness/lethargy</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Grogginess</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

\*Data are presented as number of adverse events (number of subjects).
Further research will need to determine if the SWS-enhancing effect of tiagabine persists beyond a few nights and if a qualitative difference in sleep can be demonstrated relative to either baseline sleep or sleep with benzodiazepine-receptor agonists. The effects of tiagabine 8 mg on the ratio of stage 3+4 sleep/(stage 1 sleep + WASO) may relate to the reduced number of subject-reported awakenings in the 8-mg condition, although other self-report measures did not vary across conditions. It will also be interesting to determine if self-reported aspects of sleep improve with longer-term use.

The effects of tiagabine on sleep in this study are consistent with those of a double-blind, placebo-controlled study in 10 healthy elderly adults, in which tiagabine 5 mg significantly increased TST and SWS and improved sleep efficiency compared with placebo.3

The frequency of central nervous system adverse events and the slightly poorer delayed-recall performance in the morning suggest that a proportion of elderly individuals may not tolerate doses of 8 mg or more. On the other hand the delayed-memory difference may be a chance finding because other morning-impairment measures (Digit Symbol Substitution Test, immediate recall, Karolinska Sleepiness Scale, and ratings of alertness level and ability to concentrate) did not reveal a deficit, nor a consistent direction of effect. Only studies that include significantly larger sample sizes will provide a clear assessment of the therapeutic ratio of various doses of tiagabine in elderly individuals.

The most reliable pharmacologic effect of tiagabine appears to be an increase in SWS, with an apparently linear dose effect and a 2-fold increase in absolute minutes of SWS in the T8 condition compared with placebo. The increases in SWS at the 8-mg dose occurred in conjunction with a significant reduction in minutes of stage 1 and REM sleep. The biologic and/or clinical significance of pharmacologically mediated increases in SWS remains to be elucidated but conceivably may relate to the homeostatic mechanisms involved in SWS regulation. The reduced SWS latency and reduced WASO and stage 1 sleep, in addition to the increased amount of SWS, are consistent with changes in sleep as a result of sleep deprivation.14-16 The hypothesized importance of SWS for restoration7,18 raises the question if tiagabine, or other drugs that significantly increase SWS, may enhance the restorative properties of sleep. Similarly the reduction in REM sleep, although relatively small compared with the increase in SWS (15% decline in REM with 8-mg vs placebo; 100% increase in SWS with 8-mg vs placebo) may not be without significance and should be evaluated.

In conclusion, the results of this study showed that tiagabine 4 and 8 mg improved sleep maintenance by decreasing WASO and/or stage 1 sleep, as well as increasing SWS. Further research with tiagabine at dosages of 8 mg or less appears warranted in elderly clinical populations.

ACKNOWLEDGMENTS

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REFERENCES