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Original article

Tiagabine enhances slow wave sleep and sleep maintenance in primary insomnia

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Abstract

Background and purpose: To evaluate the effect of tiagabine on sleep and next-morning alertness and performance in adult patients with primary insomnia.

Patients and methods: Patients with primary insomnia, as defined by Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV), received tiagabine 4, 8, 12, 16 mg, and placebo in a randomized, double-blind, five-period, Latin square, crossover study. Efficacy was assessed using polysomnographic and self-report techniques; residual effects were evaluated using the Digit Symbol Substitution Test (DSST) and the Rey Auditory Verbal Learning Test (RAVLT).

Results: Fifty-eight patients (40f, 18m; mean age 46.6 ± 8.0 years) were randomized. Results showed a significant dose-dependent increase in slow wave sleep percentage with all tiagabine doses, a trend toward a dose-dependent increase in total sleep time, and no effect on latency to persistent sleep. Wake after sleep onset also decreased in a dose-dependent manner, with the 16-mg dose differing significantly from placebo. The tolerability profiles of tiagabine 4 and 8 mg were similar to placebo. The most common adverse events reported following tiagabine 12 and 16 mg were dizziness and nausea. Residual effects were only apparent at 12- and 16-mg doses.

Conclusions: Tiagabine increased slow wave sleep and reduced wake after sleep onset in a dose-dependent manner. Tiagabine dosages up to 8 mg did not compromise next-morning alertness and psychomotor performance in adult patients with primary insomnia. Further investigation of tiagabine doses up to 8 mg is warranted.

Keywords: Primary insomnia; Sleep maintenance; Slow wave sleep; Wake after sleep onset; Sleep efficiency; Tiagabine

1. Introduction

Primary insomnia is characterized by difficulty initiating or maintaining sleep and/or nonrestorative sleep, which causes clinically significant distress or impairment in important areas of waking function [1]. Most investigations of pharmacotherapy for primary insomnia have involved a benzodiazepine receptor agonist (BzRA). All BzRA hypnotics promote sleep onset, but most have not reliably improved objective measures of sleep maintenance, including wake after sleep onset [2]. In addition, most BzRA hypnotics have been found to reduce slow wave sleep (stage 3 + 4 sleep) or suppress rapid eye movement (REM) sleep [2].

Tiagabine, a selective γ-aminobutyric acid (GABA) reuptake inhibitor (SGRI), increases synaptic GABA availability through selective inhibition of the GAT-1 GABA transporter [3,4]. Tiagabine is rapidly absorbed, with a t_{max} of about 45 min in the fasting state. The rate but not the extent of absorption is reduced when ingested with food. Tiagabine has an elimination $t_{1/2}$ of 7–9 h. In the US, tiagabine is approved as adjunctive therapy for partial seizures. The recommended starting dose for adults

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is 4 mg/day with weekly increasing doses (by 4–8 mg) until a clinical response is achieved or until a daily dose of 56 mg is reached.

Since GABA is a major inhibitory neurotransmitter in the central nervous system and tiagabine increases synaptic availability of GABA, hypnotic properties would seem a likely dose-related effect. Indeed, dizziness and somnolence, commonly noted with hypnotic medications, are two of the more common adverse events in epilepsy trials with tiagabine. Subjective improvements in sleep have been reported during open-label use of tiagabine in patients with posttraumatic stress disorder [5] and generalized anxiety disorder [6].

In a study of healthy elderly subjects, tiagabine 5 mg significantly increased slow wave sleep and improved sleep efficiency by reducing wakefulness during the sleep period [7]. This finding was consistent with a preclinical investigation that documented increased slow wave activity in the rat [8]. The objective of the present study was to evaluate the effect of tiagabine administered before bedtime at doses from 4 to 16 mg on sleep and next-morning alertness and psychomotor performance in adult patients with primary insomnia.

2. Methods

2.1. Study design and general procedures

This randomized, double-blind, placebo-controlled, five-period, crossover study was conducted at nine sleep laboratories in the United States. Patients with primary insomnia received tiagabine 4, 8, 12, 16 mg, and placebo according to a Latin square design. The study included a clinical screening visit to ensure that patients met all inclusion and exclusion criteria, two consecutive polysomnography screening nights, and, following randomization, two consecutive polysomnography nights for each of the five doses (i.e. five assessment periods). The assessment periods were separated by 5–12 nights of sleep at home without study drug. A post-study safety evaluation was performed after all treatment nights were completed. The protocol was approved by institutional review boards for each site. All patients provided written consent and were paid for participating in the study. The study was performed in accordance with the Declaration of Helsinki and complied with Good Clinical Practice guidelines.

2.2. Patients and screening procedures

Male and female patients, aged 35–64 years, were recruited to participate in the study. The lower age limit of 35 was selected because a decline in slow wave sleep begins, particularly in males, around this age [9]. After telephone screening, potential participants were screened at an initial clinic visit that included a medical, sleep, and psychiatric history, physical examination, and clinical laboratory evaluations. These procedures allowed the inclusion of patients who fulfilled the following criteria: (1) a Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) diagnosis of primary insomnia; (2) self-report of the following insomnia symptoms at least three nights per week over the preceding month: ≥ 3 nocturnal awakenings or wake after sleep onset of ≥ 60 min; sleep latency of ≥ 30 min; and total sleep time of < 6 h; and (3) self-report of 6.5 to 9 h in bed at least five nights/week with a habitual bedtime between 2100 and 0100.

Exclusion criteria were as follows: (1) any clinically significant unstable medical condition; (2) DSM-IV axis-I psychiatric disorder other than primary insomnia, e.g. major depressive disorder; (3) a history of substance abuse; (4) any disorder that may interfere with drug pharmacokinetics; (5) use of any medication that may affect sleep-wake function; (6) use of any CYP3A4 inducer/inhibitor; (7) napping ≥ 3 times a week; (8) consuming ≥ 500 mg per day of xanthine-containing food or beverages; (9) consuming > 14 units of alcohol (1 unit = 8 oz beer, 3 oz wine, or 1 oz hard liquor) in any one week or > 5 units of alcohol in any one day during the preceding month; (10) smoking > 1 pack of cigarettes per day, or being unable to stop smoking during time in the sleep laboratory; (11) being pregnant or lactating; (12) having a body mass index > 34 (kg/m^2); (13) performing shift work; or (14) traveling across > 3 time zones in the past two weeks.

Individuals meeting all entry criteria at the initial visit were scheduled within one week for polysomnography screening on two consecutive nights, with single-blind placebo administered 30 min before lights out. For all recordings, time in bed was 480 min; lights out time for each patient was within 30 min of his or her habitual bedtime and held constant throughout the study. On the first screening night, patients were evaluated for sleep apnea (exclusion: apnea/hypopnea ≥ 10/h) and periodic limb movement disorder (exclusion: periodic limb movement arousals ≥ 10/h). Polysomnography entry criteria were as follows: mean latency to persistent sleep ≥ 20 min, with neither screening night value < 15 min; mean wake after sleep onset ≥ 40 min, with neither screening night < 25 min; and total sleep time of > 3 and ≤ 7 h on both nights.

2.3. Experimental procedures

Following randomization, each dose of study drug was administered 30 min before the start of the recording on two consecutive nights, with a 5- to 12-day washout period with sleep at home between assessment periods. Standard techniques [10] were used and scoring was performed at a centralized site, according to standard criteria [11]. Patient estimates of sleep were obtained using a post-sleep questionnaire, which was completed within 30 min of rise time. Safety was assessed at each visit using patient-reported adverse events and vital signs. In addition, morning sleepiness/alertness was assessed using a visual analogue