Acute Effects of Mirtazapine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study

Andrew Winokur, Michael J. Sateia, J. Boyd Hayes, Wendy Bayles-Dazet, Mary M. MacDonald, and Keith A. Gary

Background: Mirtazapine, a clinically effective antidepressant, acts by antagonizing central α₂-adrenergic and 5-HT₂/5-HT₃ receptors. No data are available regarding mirtazapine’s effects on sleep architecture in patients with major depressive disorder.

Methods: Six patients meeting criteria for major depressive disorder and scoring ≥4 on the three Hamilton Depression Rating Scale sleep items were studied. Polysomnographic evaluations were performed at baseline and after 1 (15 mg at bedtime) and 2 weeks (30 mg at bedtime) of open-label mirtazapine treatment.

Results: Mirtazapine significantly decreased sleep latency and significantly increased total sleep time and sleep efficiency from baseline levels during week 1, with similar results observed after week 2. Mirtazapine did not significantly alter rapid eye movement sleep parameters. Clinically, Hamilton Depression Rating Scale and sleep disturbance ratings improved after treatment.

Conclusions: Mirtazapine significantly improves sleep continuity in major depressive disorder patients with poor sleep quality at weeks 1 and 2 of treatment, while preserving sleep architecture.

Key Words: Polysomnography, depression, insomnia

Introduction

The majority of major depressive disorder (MDD) patients subjectively report prolonged sleep onset and/or disturbed sleep continuity as the most prevalent symptoms (Winokur and Reynolds 1994). Objective polysomnographic (PSG) analysis of depressed patients reveals disrupted sleep continuity, altered rapid eye movement (REM) sleep timing, and reductions in slow-wave sleep (SWS) quantity (Kupfer and Reynolds 1992). Additionally, antidepressant drug administration elicits pronounced differences in PSG measures of sleep continuity and sleep architecture (Winokur and Reynolds 1994). Sedating antidepressants shorten sleep latency and improve sleep continuity, whereas more activating antidepressants prolong sleep latency and impair sleep continuity measures. Sleep architecture also may be differentially altered by antidepressant drugs (e.g., whereas many antidepressants potently suppress REM sleep, a few do not, despite similar efficacies in treating depression).

Effects of antidepressant drugs on sleep parameters are clinically relevant due to the frequency of sleep complaints in depressed patients. Although controlled studies have not evaluated sleep disorder symptoms as criteria in antidepressant drug selection for specific patients to enhance treatment outcome, clinical experience suggests this may represent an important basis for treatment selection.

The novel α₂-adrenergic and 5-HT₂/5-HT₃ receptor antagonist, mirtazapine, is a clinically effective antidepressant drug (Claghorn et al 1987; Pinder 1997). Subjective complaints of sleep disturbances improved significantly and rapidly in placebo-controlled studies of depressed patients treated with mirtazapine. Conversely, over half of patients receiving mirtazapine treatment reported daytime somnolence, as compared with 18% in patients randomized to a placebo (Organon 1996). These observations suggest that laboratory studies of mirtazapine’s effects on sleep physiology are important in guiding optimal use of this compound; yet, to date, only a single PSG study has examined mirtazapine. Ruigt et al (1990) administered mirtazapine (30 mg) or a placebo at 9:00 PM to six healthy subjects and observed decreased sleep latency, increased total sleep time, and reduced stage 1 sleep and increased stage 3 sleep, indicative of deeper sleep in treated subjects.

In this open-label study we examine the acute effects of 1- and 2-week mirtazapine administration on sleep continuity and sleep architecture variables by employing PSG techniques and subjective sleep measures in six patients with MDD accompanied by subjective sleep complaints.

Methods and Materials

Subjects were recruited from the Psychiatry Department at Dartmouth Hitchcock Medical Center and from respondents to newspa-
per advertisements. Six patients provided informed consent, enrolled, and successfully completed the study. Patients were required to meet the following criteria: 18–65 years of age with a DSM-IV diagnosis of MDD based upon a semistructured interview; a score of \( \geq 18 \) on the 17-item Hamilton Depression Rating Scale (HDRS), and a score of \( \geq 4 \) on the three HDRS sleep items (Hamilton 1960). Patients with a history of primary sleep disorder, significant medical problems, current alcohol or substance abuse, psychosis, suicidal ideation, and those performing shift work were excluded from the study. Patients were screened for “normal” sleep/wake schedules, with typical bed times no earlier than 10:00 PM or risings earlier than 6:00 AM, and identical schedules maintained in the sleep laboratory. Psychotropic drugs were discontinued at least 1 week before study initiation, and no subject had been taking fluoxetine or other central nervous system agents with prolonged effects in the previous month.

Polysomnography consisted of bilateral monopolar central electroencephalogram (EEG) recording and occipital EEG (C3/A2, C4/A1, and Oz/A1), bilateral electrooculogram, and submental electromylogram. Single-channel electrocardiogram was monitored and sleep studies scored per standard Rechtschaffen and Kales criteria (Rechtschaffen and Kales 1968). After initial clinical assessment and HDRS administration subjects underwent 2 nights of baseline PSG monitoring. Mirtazapine administration (15 mg at bedtime [h.s.]) was initiated and 2 nights of PSG repeated at the end of week 1. Clinical assessment, adverse event evaluation, and HDRS ratings were repeated, and the Clinical Global Improvement (CGI) scale employed, between the 2 PSG nights (Guy 1976). The CGI reflects clinical global improvement on a scale of 0, no change; 1, slight improvement; 2, moderate improvement; and 3, marked improvement. Mirtazapine dosage was then increased to 30 mg h.s., and 2-night PSG, clinical assessment, HDRS, and CGI ratings repeated at the end of week two. Clinical treatment response was determined by clinical assessments, HDRS, and CGI performed at weeks 4 and 6.

Polysomnographic data included total sleep time, sleep efficiency (total sleep time/time in bed), and sleep latency (onset to first stage 1) as a priori primary variables, and total sleep time and percentage of total sleep time for stages 1, 2, 3, and 4; stages 3 and 4 combined to represent SWS; REM; and REM latency as a priori secondary variables. Total sleep time measures for stages 1–4 were recorded to assess potential sleep stage–specific alterations induced by mirtazapine. Mean, SD, and SEM were calculated for each parameter across subjects. The means were then compared at baseline, week 1 (15 mg), and week 2 (30 mg) by one-way repeated-measures analysis of variance (SigmaStat, SPSS, Chicago). Measures achieving statistical significance (\( p < .05 \)) were analyzed post hoc by the Bonferroni method due to the relatively small number of comparisons and its increased stringency in achieving statistical significance.

**Results**

The PSG data demonstrated rapid improvement in sleep continuity measures, with significant changes from baseline observed after both treatment weeks in sleep latency [\( F(2,17) = 4.79, p = .009 \)], total sleep time [\( F(2,17) = 16.3, p = .004 \)], and sleep efficiency [\( F(2,17) = 10.1, p = .0003 \); Figure 1]. Objective improvements in sleep continuity were accompanied by improvements in HDRS and sleep disturbance scores (Table 1). Three of six subjects reported mild daytime sedation and one rated the sedation as moderate, but sedation did not worsen with dosage increase or time and was not cause for study discontinuation for any subject.

No significant changes in sleep stage distribution were observed and, specifically, no increase in SWS [\( F(2,17) = 1.87, p = .204 \)], which was low at baseline and remained low over the 2 weeks of PSG study. No significant
Changes in stage 1 percentage \(F(2,17) = 0.505, p = .62\), stage 2 percentage \(F(2,17) = 0.222, p = .806\), REM percentage \(F(2,17) = 1.12, p = .365\), total REM time \(F(2,17) = 3.93, p = .059\), or REM latency \(F(2,17) = 2.92, p = .012\; (Table 1)\) were identified.

At the end of week 2 (30 mg mirtazapine h.s.), significant improvements continued in sleep latency, total sleep time, and sleep efficiency, and improvements in HDRS ratings and sleep disturbance scores were also sustained. Despite the increased mirtazapine dose, daytime somnolence complaints diminished or abated, with only two subjects continuing to report daytime sleepiness at levels of “mild.” No significant alterations in sleep architecture were observed at the week 2 testing period, though a trend for prolonged REM latency was evident.

**Discussion**

Our results suggest that acute mirtazapine administration rapidly improves both subjective ratings of depression and objective physiologic parameters of sleep disturbance in patients with MDD accompanied by disturbed sleep. Although four of six subjects reported daytime somnolence during week 1 (15 mg), these complaints resolved by the end of week 2 (30 mg). Thus, patients may develop tolerance to mirtazapine’s sedating effects within a few days of treatment initiation. Conversely, no loss of efficacy was observed with respect to the sleep continuity measures across the 2-week period assessed.

The mechanisms underlying mirtazapine’s sleep-promoting effects have not been clarified, although its pharmacologic properties suggest several possibilities (Pinder 1997). Both antihistaminic and \(\alpha\)-adrenolytic actions of mirtazapine might contribute to its sleep-enhancing effects. Alternatively, the potent effects of mirtazapine may result from 5-HT\(_2\) receptor inhibition (de Boer 1996), as the 5-HT\(_2\) receptor is an important site implicated in sleep initiation and/or maintenance with particular relevance to SWS regulation (Idzikowski et al 1989). Moreover, the 5-HT\(_2\) receptor may mediate the activating effects of some selective serotonin reuptake (Stahl 1996). Further studies will be needed to explore the possible relationship between mirtazapine and the 5-HT\(_2\) receptor with respect to sleep physiology.

Our study was limited by several factors. First, inclusion of only six patients places these findings in the context of a pilot study, requiring replication and extension with a considerably larger sample size. Nevertheless, these findings constitute the first published report of mirtazapine’s effects on sleep physiology in depressed patients. Second, the treatment protocol was conducted in an open fashion without a placebo control group, limiting the interpretability of the treatment response data (though extensive double-blind treatment response data for mirtazapine have previously been presented) and, arguably, of the findings pertaining to the sleep physiology parameters. Finally, mirtazapine’s effects on daytime sleepiness were obtained exclusively from subjective patient reports, without objective assessments of daytime sleepiness.

Despite study limitations, the results suggest several intriguing implications. Both depression ratings and sleep disturbance symptoms improved significantly in this patient population after 1 week of mirtazapine administration. Conceivably, rapid relief of insomnia symptoms may have contributed to the rapidity of antidepressant response. The magnitude of objective changes in sleep continuity
parameters produced by mirtazapine was strikingly large, with total sleep time increased by over 1 hour after week 1 and associated with a 9% increase in sleep efficiency. These increases in sleep continuity parameters are larger than generally reported in PSG-monitored studies of antidepressant drug treatment (Rush et al 1998) and compare favorably to effects reported for specific hypnotic agents developed for primary insomnia treatment. Thus, additional studies examining mirtazapine’s short- and long-term effects on sleep parameters both in depressed patients with coexisting insomnia and in individuals with subjective complaints of insomnia for other reasons are warranted.

Funding provided by an unrestricted educational grant from Organon Inc. (AW).

References


