The Effects of Mirtazapine on Sleep: A Placebo Controlled, Double-Blind Study in Young Healthy Volunteers

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Study objectives: Mirtazapine is classified as a noradrenergic and specific serotonergic antidepressant. This study aims at objectively investigating the effects of single-dose mirtazapine on sleep of healthy volunteers.

Design and Setting: We studied the effect of acute administration of mirtazapine (30 mg) on the sleep polysomnogram, using a double-blind, placebo-controlled design. Subjects spent 3 consecutive nights in the laboratory. First night allowed for adaptation to the laboratory and application of electroencephalogram electrodes, while the second and third nights were reserved for recording baseline sleep and studying the effects of drug treatment, respectively.

Participants: Young healthy volunteers (n=20), with a mean age of 24 years, were randomly separated into two groups: placebo (n= 10) and mirtazapine (n=10).

Interventions: On the third night, subjects received either placebo or mirtazapine. Comparisons were made between sleep variables from baseline values in both groups. Independent samples *t*-test was utilized to evaluate the differences between the two groups.

Measurement and Results: Mirtazapine improved the variables related to sleep continuity when compared with placebo. It increased the sleep efficiency index, while decreasing the number of awakenings and their duration. The slow wave sleep time was increased, while the stage 1 sleep time was decreased significantly. There was no significant effect on rapid eye movement sleep variables.

Conclusion: Our findings suggest that mirtazapine has considerable effects on slow wave sleep. Further studies are recommended to investigate the efficiency of antidepressants, in respect to the effects of 5-HT_2 blockade on slow wave sleep.

Key words: Mirtazapine; antidepressants; polysomnography; sleep; single dose; healthy volunteers

INTRODUCTION

ANTIDEPRESSANT DRUGS OFTEN INDUCE CHANGES IN THE SLEEP POLYSOMNOGRAM. The duration of rapid eye movement (REM) sleep is reduced and its onset latency is prolonged.[1] The existence of a correlation between the antidepressant and REM-suppressing effects of these drugs has already been suggested.[2-4] However, drugs that display antidepressant effects without REM-sleep suppression are known to exist; nefazodone, trimipramine, trazodone, bupropion, moclobemide, and mirtazapine are some of the examples.[5-7]

Mirtazapine, being a noradrenergic, specific serotonergic drug, is classified as a tetracyclic antidepressant in the piperazine group. It specifically antagonizes central α_2 adrenergic, as well as 5-HT_2 and 5-HT_3 serotonergic receptors, which results in the potentiation of central noradrenergic and serotonergic neurotransmission, producing a clinical antidepressant effect. When compared with selective serotonin reuptake inhibitors (SSRIs), it has fewer undesired effects such as insomnia, sexual dysfunction, and nausea, due to its selective blocking properties on postsynaptic neurons. Mirtazapine appears to be equivalent in efficacy to tricyclic antidepressants.[8] One placebo-controlled study, investigating the immediate effects of a single dose of oral mirtazapine, demonstrated its lack of ability to significantly prolong REM latency and suppress REM sleep, despite observation of a trend toward an increase in REM latency.[6] These results suggest that mirtazapine mediates its antidepressant activity through a mechanism other than REM suppression, while a literature search reveals no conclusive evidence on the issue. The aim of the present study was to objectively assess the effects of mirtazapine, a new antidepressant drug, on sleep patterns of young healthy adults.

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METHODS

Subjects

After approval of the study protocol by the local ethics committee, a total of 20 young adult volunteers, with a mean age of 24 (range, 18-30 years) were recruited from a group who responded a newspaper ad. Subjects read and signed a consent form. They were in good physical health as determined by physical examination and clinical laboratory tests. On the basis of a clinical interview, Hamilton Depression[9] and Hamilton Anxiety Scales,[10] all subjects were found to be free of depression and anxiety. Exclusion criteria included chronic mental illness, treatment with psychoactive medication in the previous year, tobacco or substance addiction, and a history of extreme stress in the previous month. Sleep history and diary were also obtained. Abnormal sleep patterns, such as staying up and waking up late, reduced (<6 hours) or prolonged (>10 hours) sleep time, segmented sleep, sleep onset latency greater than 30 minutes, or an antecedent history of a sleep disorder (insomnia, hypersomnia, restless legs, nocturnal myoclonus, parasomnias, etc.) led to exclusion from the study.

Design

Subjects were randomly allocated to receive either mirtazapine (n=10) or placebo (n=10) in a double-blind manner. There were 7 male and 3 female subjects in the mirtazapine group, while the age-matched placebo group consisted of 5 male and 5 female volunteers. Identically appearing tablets of mirtazapine (30 mg) or placebo were given at 10.30

Table 1—Baseline sleep measures and comparison of treatment effects on baseline values

Variable	BASELINE		DIFFERENCES FROM BASELINE		
	Placebo Mean±SD	Mirtazapine Mean±SD	Placebo Mean±SD	Mirtazapine Mean±SD	Sig.
Time Spent in Bed (min)	427.0 ± 34.5	445.0 ± 22.2	30.2 ± 32.8	8.6 ± 31.9	NS
Sleep Period Time (min)	410.9 ± 34.3	426.4 ± 21.1	26.9 ± 33.7	19.7 ± 31.6	NS
Total Sleep Time (min)	401.4 ± 30.4	415.3 ± 21.8	28.2 ± 30.5	29.4 ± 32.0	NS
Sleep Onset Latency (min)	12.1 ± 7.5	11.7 ± 7.2	2.4 ± 14.5	-4.4 ± 8.4	NS
Sleep Efficiency Index	94±3.0	93 ± 3.3	1 ±0.4	5 ± 0.4	0.017*
Number of Awakenings	2.0 ± 1.6	3.7 ± 2.8	0.1 ± 1.4	-2.5±2.5	0.012*
Wake Time After Sleep Onset (min)	5.4 ± 4.5	13.4 ± 11.0	2.7 ± 5.5	-12.0±10.8	0.001*
Wake Time After Final Awakenings (min)	7.8±10.7	4.4 ±12.5	-2.7 ± 11.4	-4.2±12.6	NS
REM Latency (min)	106.5 ± 39.4	138.5 ± 26.1	7.4 ± 50.9	50.2 ± 60.8	NS
Total REM Sleep Time (min)	101.4 ± 18.9	79.4 ±21.7	-9.8 ± 28.3	-6.6±27.9	NS
Percentage of REM Sleep	25 ± 6	19 ± 5	-4 ±7	-3 ± 7	NS
Stage 1 Sleep Time (min)	13.5 ± 9.1	29.4 ± 19.1	6.4 ± 18.0	-12.4 ± 20.5	0.0043*
Stage 2 Sleep Time (min)	218.3 ± 43.7	233.5 ± 30.6	31.7±39.0	17.3±41.9	NS
Stage 3 Sleep Time (min)	33.5 ± 14.2	40.3 ± 18.7	-0.7 ± 19.4	27.1 ± 44.8	0.045*
Stage 4 Sleep Time (min)	37.1 ± 29.2	35.1 ± 24.3	4.2 ± 29.5	9.1 ± 37.7	NS
Total Slow Wave Sleep Time (min)	71.4 ± 26.6	75.9 ± 25.6	-4.0 ± 22.9	36.8 ± 51.2	0.034*
Percentage of Slow Wave Sleep	17.9 ± 6	18.3 ± 6.2	-2 ± 6	7 ± 1	0.033*
REM Sleep Time in the first ½ part of night (min)	22.4 ± 9.3	28.0 ± 22.1	4.1 ± 20.8	-16.7 ± 24.9	NS
REM Sleep Time in the second ½ part of night (min)	79.0 ± 15.3	51.0 ± 25.7	-8.0 ± 20.7	10.5 ± 31.8	NS
Non-REM Sleep Time in the first ½ part of night (min)	178.2 ± 22.0	175.8 ± 29.8	13.7±24.6	32.2±35.2	NS
Non-REM Sleep Time in the second ½ part of night (min)	123.1 ± 26.7	161.7 ± 25.7	22.5±32.9	2.5±35.6	NS
Slow Wave Sleep Time in first ½ part of night (min)	49.4 ± 24.6	50.3 ± 18.9	5.7±34.1	40.9±52.6	NS
Slow Wave Sleep Time in second ½ part of night (min)	11.2 ± 12.6	25.3 ± 13.2	5.7±19.6	-3.9±15.4	NS

min, minutes; NS, not significant; SD, standard deviation; SIG, significance; REM, rapid eye movement; * $p<0.05$, significantly different from placebo, differences between baseline and treatment values were compared.

h, half an hour before the start of overnight electroencephalogram (EEG) recording. Sleep recordings were carried out on 3 consecutive nights in the following order: a) adaptation to the "first night effect," b) "baseline" sleep evaluation, and c) investigation of either drug or placebo effects. Subjects completed a presleep questionnaire each night, asking their daily activities, emotional state, and whether they had used alcohol or caffeine. In the morning, another questionnaire was completed concerning how they had slept. Although subjects were requested to refrain from using alcohol for the duration of the study, a few cigarettes during daytime and consumption of small amounts of caffeinated drinks before 4 p.m. were allowed. They had also been instructed to not take medications and naps on study days.

Polysomnographic recordings

Electrodes were applied at 20.00 h upon arrival to the laboratory. The EEG recordings started at 23.00 h and the lights were turned off. Subjects were allowed to sleep undisturbed throughout the night, and they rose at their usual time, but time in bed was not kept constant. Two-channel polysomnographic EEG monitoring was used in the following montages: C3-A2 or C4-A1 and O1-A2 or O2-A1. The electroculogram (EOG) and electromyographic (EMG) activity were also recorded. High- and low-frequency filter settings were 30 and 0.1 Hz, respectively, for EEG and EOG, and 120 and 10 Hz for EMG. Paper speed was 10 mm per second. Sensitivity on the EEG and EOG channels was 10 µV/mm and 7.1 µV/mm respectively. Polygraphic records were analysed and scored visually according to established criteria,[11] without prior knowledge of the identity of the subjects. Sleep onset was defined as the end of at least 3 consecutive epochs of stage 1 or the beginning of stage 2 sleep. Slow wave sleep was characterised by sleep stages 3 and 4 combined.

Statistical Analysis

Sleep variables analysed by using one-sample Kolmogorov-Smirnov test revealed no skewed or otherwise nonnormal distributions. Intergroup differences between baseline sleep variables and effects of placebo or drug administration on baseline values were calculated by means of a two-tailed Students *t*-test.

RESULTS

Sleep Continuity Measures

Although a significant prolongation of wake time after sleep onset in mirtazapine group (t=-2.1, p=0.048) at baseline was noted, it was decreased by the administration of the drug, which also decreased the number of awakenings, while the sleep efficiency index was significantly increased ($p<0.05$). Statistical analysis showed no effects of mirtazapine on time spent in bed, sleep-period time, total sleep time, sleep-onset latency, and wake time after final awakenings (Table).

REM Sleep Measures

A significant baseline REM latency (REML) prolongation (t=-2.1, p=0.046), as well as total REM sleep time (TREM) (t=2.4, p=0.027) and percentage (REM%) (t=2.6, p=0.016) reduction was observed in subjects allocated to the mirtazapine group. The REM sleep time in the second half of night (REM2) was also shorter in this group (t=2.9, p=0.009). The TREM, REM%, REML, REM sleep time in the first half of night, and REM2 showed no significant suppression with mirtazapine.

Non-REM Sleep Measures

At baseline, stage 1 sleep time (t=-2.3, p=0.023), slow wave sleep time in the second half of night (t=-2.4, p=0.025) and non-REM sleep time in the second half of night (t=-3.3, p=0.004) was significantly prolonged in the mirtazapine group. Although mirtazapine significantly increased the duration of stage 3 and slow wave sleep, as well as the percentage of slow wave sleep ($p<0.05$), when analysed separately the effect on the duration of slow wave sleep time in the first half of night and second half was not significant. Stage 1 sleep time was significantly reduced by mirtazapine administration (p<0.05) (Table). Stage 2 sleep time, non-REM sleep time in the first and in the second half of the night were not affected significantly by the drug (Table).

DISCUSSION

Mirtazapine increased the sleep efficiency and enhanced the sleep continuity, as previously reported by Ruight et al on 6 volunteer subjects.[6] Our finding of a lack of REM-sleep suppression is supported by

their results. They found a slight, but nonsignificant reduction in the duration of REM sleep and prolongation of REM-sleep latency. Mirtazapine did not decrease the percentage of REM sleep.[6] Tricyclic antidepressants, SSRIs and monoamine oxidase inhibitors (MAOIs) strongly suppress REM-sleep latency.[1,5,12] In our study, we could not demonstrate a significant REM-sleep-suppressing effect of mirtazapine. Due to its distinct effects on human sleep, this compound merits a separate classification.

The effects of mirtazapine were also notable for a significant increase in slow wave sleep. Although some antidepressants such as clomipramine, trazodone, and ritanserine (a specific antagonist of 5-HT_2 receptors) have been reported to increase the slow wave sleep,[13-16] SSRIs and MAOIs have very little or no effect on it.[1,17-19] Mirtazapine may produce its effects by deepening the sleep in patients with depression. While some studies report an association of increased deep sleep with antidepressant effect,[13,15] a clear knowledge on such a relation is lacking. Although the neurochemical basis for this effect of mirtazapine is unknown, it may be related to its 5-HT_2-receptor antagonism[8,16] Other 5-HT_2 blockers such as nefazodone also lack the sleep-disturbing effects of SSRIs.[7,20] The deepening of sleep after 5-HT_2 antagonism may be of particular help in depressed patients and should be studied further.

Our study has two important limitations. Primarily, the number of our subjects may have been insufficient to evaluate the effects of the drug on REM sleep. Our groups of 10 individuals each showed a power of 56% and 64% respectively, to detect a difference from baseline values in REM latency and total REM time. A power analysis regarding the number needed to have an 80% power to reveal REM-latency and REM-time differences from baseline showed that at least 17 and 14 subjects were required, respectively. However, recruitment of healthy subjects was difficult, and we had to carry out the study on a limited number of individuals. The second concern is the significantly suppressed baseline REM parameters in the mirtazapine group, which might have produced a bias against observing drug effects on REM sleep. Further studies are needed to reach conclusive decisions on REM-suppressing effects of this drug.

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