Risperidone Augmentation Decreases Rapid Eye Movement Sleep and Decreases Wake in Treatment-Resistant Depressed Patients

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Background: The atypical antipsychotic agent risperidone has beneficial effects on mood in patients with schizophrenia. This study aimed to assess whether risperidone produced typical antidepressant-like effects in the polysomnogram of healthy subjects and in depressed patients unresponsive to antidepressant medication.

Method: We measured the effect of a single dose of risperidone (1 mg) on the polysomnogram of 8 healthy volunteers in a placebo-controlled, double-blind, crossover design. We also measured the effects of open-label risperidone treatment (0.5–1.0 mg daily) on the polysomnogram of 8 patients meeting DSM-IV criteria for major depressive disorder who had received therapeutic doses of an antidepressant with an unsatisfactory response. Sleep was recorded at baseline and following 2 weeks of risperidone addition.

Results: In the healthy volunteers, risperidone significantly decreased rapid eye movement (REM) sleep ($p = .04$). After 2 weeks of risperidone treatment, depressed patients had significantly less wake ($p = .02$) and REM sleep ($p = .02$). Scores on depression rating scales for the depressed patients showed a significant decline ($p < .05$).

Conclusion: Risperidone administration decreases REM sleep in both healthy volunteers and medication-resistant depressed patients, an action characteristic of conventional antidepressant medication. In depressed patients, risperidone also decreased wake. The utility of risperidone as an augmentation agent in depressed patients merits controlled study.

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Risperidone is an atypical antipsychotic drug that potently antagonizes serotonin-2A/2C ($5\text{-}HT_{2A/2C}$) and dopaminergic D_2 receptors.[1,2] Risperidone has beneficial effects on mood in patients with schizophrenia[3] and may produce a lower incidence of sleep disturbance than conventional antipsychotic drugs.[4] A case series indicated that risperidone produced rapid improvement in mood, with beneficial effects on subjective sleep, in 8 patients with major depression who had failed to respond fully to treatment with selective serotonin reuptake inhibitors.[5] Interestingly, this effect was seen at low doses of risperidone (0.5–1.0 mg) that would be expected to produce relatively preferential blockade of central $5\text{-}HT_2$ receptors.[1]

Drugs that have antidepressant effects typically decrease the amount of rapid eye movement (REM) sleep in the polysomnogram. The aim of the present study was to test the hypothesis that low-dose risperidone would decrease REM sleep both in healthy volunteers and in depressed patients who had failed to respond to antidepressant treatment. In addition, we predicted that in the depressed patients, risperidone would improve measures of sleep continuity and decrease observer and self-rated scores of depression.

METHODS AND MATERIALS

Subjects and Medication

We studied 8 healthy volunteers (4 women, 4 men; mean age = 37.6 years; range, 27–55 years) who were determined by clinical interview (nonpatient version of the Structured Clinical Interview for DSM-IV[6]) to have no current or past history of psychiatric disorder or sleep disorder and were not taking any medication. Each subject took placebo and risperidone (1 mg), once orally, 90 minutes before retiring to sleep in a double-blind, balanced-order, crossover design, with a 7- to 14-day washout period between each sleep polysomnogram.

We also studied 8 patients (7 women, 1 man; mean age = 35.6 years; range, 21–52 years) referred from primary care sources who, on the basis of a semistructured clinical interview, met DSM-IV criteria for unipolar major

depressive disorder. None had any psychotic features. They had been treated with therapeutic doses of an antidepressant for at least 6 weeks and had shown an unsatisfactory response as determined by their treating clinician. Of the 8 subjects, 7 had failed to respond to a single current antidepressant trial while the remaining subject had failed to respond to 2 antidepressant medications. Their mean score on the Hamilton Rating Scale for Depression (HAM-D)[7] was 20.6 (range, 10–27), while on the Beck Depression Inventory (BDI),[8] it was 28.9 (range, 19–43). The antidepressant treatment was as follows: fluoxetine 60 mg, N = 2; fluoxetine 40 mg, N = 2; paroxetine 30 mg, N = 1; venlafaxine 300 mg, N = 1; lofepramine 140 mg, N = 1; and citalopram 10 mg, N = 1. Patients were treated with risperidone, 0.5 mg, at night initially, increasing to 1 mg at the discretion of the treating clinician. Polysomnogram recordings were made on 2 occasions, at baseline and following 2 weeks of risperidone treatment. Ethical approval was obtained from the local ethics committee, and informed written consent was obtained from each subject.

Polysomnogram Recordings

On each study night, sleep polysomnograms were recorded as each subject slept at home, using the Oxford Medilog 9200-II cassette monitoring and sleep staging system (Oxford Instruments Medical, Surrey, U.K.). Subjects retired and rose at their usual time, and this was kept constant for all study nights and all preceding nights. Subjects refrained from alcohol on the preceding and study nights, but normal caffeine intake was maintained. Sleep montage electrodes (2 electroencephalogram channels: C_4-A_1, C_3-A_2, 2 electro-oculogram channels from the outer canthus of each eye referred to the mastoid, and submental electromyogram) were applied at approximately 1700 hours on each of the study nights. After each study night, subjects were asked to record how well they had slept. This subjective sleep quality scale consisted of 5 points, from "much better than usual" (1) to "much worse than usual" (5). Polysomnograms were staged in 30-second epochs using the Oxford Medilog 9200-II cassette monitoring and sleep staging system, which provides measures for all aspects of sleep architecture according to standard criteria.[9] In addition, the tapes were visually inspected and edited by a scorer blind to treatment status according to the criteria of Rechtschaffen and Kales.[9]

Sleep onset was defined as the beginning of the first 2 minutes that were not scored as wake or movement. Latencies to each sleep stage were calculated to the first 2 continuous minutes of the stage. We have previously demonstrated that the use of home sleep recordings and automatic analysis provides a reliable and valid means of detecting the effects of drugs on sleep architecture, including the effects on REM sleep latency.[10,11]

Statistical Analysis

Data were analyzed using SPSS for Windows (Version 9; SPSS, Inc., Chicago, Ill.). Differences between the pairs of sleep nights were assessed using the Student paired t test (2-tailed). Correlations between changes in HAM-D scores, BDI scores, and the significant sleep parameters were carried out using the Pearson product moment correlation (2-tailed).

RESULTS

Volunteer Study

In healthy volunteers, a single dose of risperidone (1 mg) significantly decreased mean ± SD REM sleep (placebo, 86.6 ± 40.0 minutes; risperidone, 59.4 ± 19.2 minutes; $p = .04$) (Table 1). No other significant differences were noted, although there was a trend toward increased stage 2 sleep (placebo, 163.7 ± 26.4 minutes; risperidone, 188.8 ± 42.2 minutes; $p = .07$).

Patient Study

After 2 weeks of risperidone treatment (final mean dose = 0.7 mg), patients had significantly less wake (baseline, 60.6 ± 23.5 minutes; risperidone, 31.8 ± 13.3 minutes; $p = .02$) and REM sleep (baseline, 107.1 ± 46.4 minutes; risperidone, 66.3 ± 55.4 minutes; $p = .02$) and significantly more stage 2 sleep (baseline, 172.3 ± 43.7 minutes; risperidone, 232.9 ± 36.7 minutes; $p = .001$) (Table 2). No other significant differences were noted, although there was a trend toward improved sleep efficiency (baseline, 81.5% ± 8.2%; risperidone, 89.1% ± 5.2%; $p = .06$). There was no significant change in subjective sleep quality (Table 2). A significant decline occurred in both HAM-D (baseline, 20.6 ± 5.6; risperidone, 11.5 ± 9.2; $p = .04$) and BDI (baseline, 28.9 ± 7.7; risperidone, 18.7 ± 11.9; $p = .02$) ratings (Table 2). There was a significant correlation between the decrease in wake and decrease in total ratings on the HAM-D (Pearson correlation = 0.727, $p = .04$). In addition, the significant correlation was maintained when only change in item 1 (depressed mood) of the HAM-D was considered (Pearson correlation = 0.725, $p = .04$). This finding indicates that the correlation between improved mood and decreased wake was not simply due to changes in the sleep items of the HAM-D.

DISCUSSION

In healthy volunteers, a single dose of risperidone (1 mg) resulted in significant REM sleep suppression, an effect produced by acute administration of most antidepressant medications in both healthy subjects and depressed patients.[12] REM sleep suppression is usually characterized by both reduction in the duration of REM sleep and an increase in the latency to REM sleep.[13–15] In the

Table 1. Effect of Risperidone, 1 mg Orally, on Polysomnogram in 8 Healthy Volunteers

Selected Sleep Parameters[a]	Group mean ± SD	Difference of Means (SD)	95% CI	t	2-Tailed Significance, p Value
Sleep continuity measures					
Total sleep time					
Placebo	429.4 ± 68.9	–5.1 (12.0)	–15.1 to 4.9	–1.208	.3
Risperidone	434.5 ± 68.8				
Sleep efficiency, %[b]					
Placebo	89.3 ± 3.8	–1.3 (4.1)	–4.7 to 2.2	–0.856	.4
Risperidone	90.5 ± 5.8				
Wake after sleep onset					
Placebo	26.9 ± 22.9	–1.4 (8.2)	–8.2 to 5.5	–0.474	.6
Risperidone	28.3 ± 26.3				
Sleep onset latency					
Placebo	16.7 ± 13.2	4.8 (11.4)	–4.7 to 14.3	1.197	.3
Risperidone	11.9 ± 8.0				
Sleep quality[c]					
Placebo	2.6 ± 0.9	0.0 (1.8)	–1.5 to 1.5	0.000	1.0
Risperidone	2.6 ± 1.3				
NREM sleep measures					
Stage 1					
Placebo	27.3 ± 11.7	–2.8 (12.7)	–13.4 to 7.8	–0.627	.6
Risperidone	30.1 ± 11.0				
Stage 2					
Placebo	163.7 ± 26.4	–25.1 (32.5)	–52.2 to 2.1	–2.180	.07
Risperidone	188.8 ± 42.2				
Slow-wave sleep					
Placebo	120.2 ± 70.2	–5.3 (29.9)	–30.3 to 19.7	–0.502	.6
Risperidone	125.5 ± 85.3				
REM sleep measures					
REM latency					
Placebo	74.9 ± 16.2	–10.7 (19.7)	–26.4 to 5.0	–1.613	.2
Risperidone	85.6 ± 27.9				
REM sleep					
Placebo	86.6 ± 40.0	27.3 (30.3)	1.9 to 52.6	2.546	.04*
Risperidone	59.4 ± 19.2				
No. of REM episodes					
Placebo	4.0 ± 1.2	0.1 (0.8)	–0.6 to 0.8	0.424	.7
Risperidone	3.9 ± 1.1				

[a]Sleep parameters expressed in minutes unless stated otherwise.
[b]Sleep efficiency = actual sleep time/time in bed × 100.
[c]Sleep quality = scores from 1 (much worse than usual) to 5 (much better than usual) on a subjective rating scale.
*Significant difference at $p < .05$.
Abbreviations: NREM = non–rapid eye movement, REM = rapid eye movement.

present study, however, risperidone did not significantly affect REM latency.

The pharmacologic mechanism by which risperidone might lower REM sleep is not clear, but a similar effect has been noted in the rat.[16] Reductions in REM sleep are associated with potentiation of norepinephrine and serotonin (5-HT) neurotransmission and also with muscarinic cholinergic blockade.[12] On the basis of studies with ritanserin, 5-$HT_{2A/2C}$ receptor blockade by itself seems unlikely to account for a decrease in REM sleep.[17,18] Risperidone does have some antagonist activity at noradrenergic α_2-adrenoceptors,[19] and α_2-adrenoceptor antagonists such as idazoxan decrease REM sleep perhaps through facilitating norepinephrine and 5-HT neurotransmission.[20]

We have recently shown[21] that single doses of another atypical antipsychotic agent, olanzapine (5–10 mg), produce substantial dose-related increases in slow-wave sleep (SWS) in healthy volunteers as well as a decrease in REM sleep. The increase in SWS seen with olanzapine is probably attributable to 5-HT_{2C} receptor blockade. The lack of effect of risperidone on this measure is consistent with ligand binding data suggesting that the affinity of risperidone for 5-HT_{2A} receptors is somewhat greater than its affinity for 5-HT_{2C} receptors.[19] Whether higher doses of risperidone might increase SWS is not clear.

In the depressed patients, 2 weeks of risperidone addition also decreased REM sleep. The patients were all taking antidepressant medications that would themselves be expected to lower REM sleep duration. However, the REM sleep time of the patients at baseline was actually greater than that of controls. The controls and patients were not age-matched, so this difference could be a chance finding. However, it is also possible that, in these patients, REM sleep had not been significantly affected by antidepressant treatment. Against this interpretation is

Table 2. Effect of Risperidone Addition on Polysomnogram in 8 Depressed Patients Receiving Antidepressant Medication

Selected Sleep Parameters[a]	Group Mean ± SD	Difference of Means (SD)	95% CI	t	2-Tailed Significance, p Value
Sleep continuity measures					
Total sleep time					
Baseline	482.1 ± 60.7	–4.8 (26.7)	–27.2 to 17.5	–0.509	.6
Risperidone	486.9 ± 59.6				
Sleep efficiency, %[b]					
Baseline	81.5 ± 8.2	–7.6 (9.5)	–15.5 to 0.3	–2.28	.06
Risperidone	89.1 ± 5.2				
Wake after sleep onset					
Baseline	60.6 ± 23.5	28.8 (26.7)	6.5 to 51.0	3.049	.02*
Risperidone	31.8 ± 13.3				
Sleep onset latency					
Baseline	19.6 ± 16.1	5.8 (13.4)	–5.4 to 17.0	1.224	.3
Risperidone	13.8 ± 11.0				
Sleep quality[c]					
Baseline	3.5 ± 0.8	0.4 (0.8)	–0.3 to 1.2	1.441	.2
Risperidone	3.1 ± 0.7				
NREM sleep measures					
Stage 1					
Baseline	45.6 ± 18.9	2.8 (30.2)	–22.5 to 28.0	0.258	.8
Risperidone	42.8 ± 17.9				
Stage 2					
Baseline	172.3 ± 43.7	–60.7 (28.9)	–84.8 to –36.6	–5.946	.001**
Risperidone	232.9 ± 36.7				
Slow-wave sleep					
Baseline	88.1 ± 40.2	–21.4 (32.3)	7.3 to 74.3	–1.871	.1
Risperidone	109.4 ± 33.6				
REM sleep measures					
REM latency					
Baseline	145.2 ± 78.9	–65.8 (125.9)	–171.0 to 39.4	–1.479	.2
Risperidone	211.0 ± 113.1				
REM sleep					
Baseline	107.1 ± 46.4	40.8 (40.1)	7.3 to 74.3	2.878	.02*
Risperidone	66.3 ± 55.4				
No. of REM episodes					
Baseline	3.3 ± 1.0	0.6 (2.0)	–1.0 to 2.3	0.886	.4
Risperidone	2.6 ± 1.5				
Depression rating scales					
HAM-D					
Baseline	20.6 ± 5.6	9.1 (9.9)	0.81 to 17.4	2.594	.04*
Risperidone	11.5 ± 9.2				
BDI					
Baseline	28.9 ± 7.7	10.1 (10.1)	1.7 to 18.6	2.834	.02*
Risperidone	18.7 ± 11.9				

[a]Sleep parameters expressed in minutes unless stated otherwise.
[b]Sleep efficiency = actual sleep time/time in bed × 100.
[c]Sleep quality = scores from 1 (much worse than usual) to 5 (much better than usual) on a subjective rating scale.
*Significant difference at $p < .05$.
**Highly significant difference at $p = .001$.
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, NREM = non–rapid eye movement, REM = rapid eye movement.

the fact that the patients did have increased latency to REM sleep and decreased REM episodes. Risperidone also decreased wake, although subjective ratings of sleep quality did not change.

Sedating antidepressants such as tricyclic antidepressants improve sleep continuity in both depressed patients and healthy subjects by decreasing wake.[22,23] Therefore, a possible explanation for the decrease in wake produced by risperidone is that the patients experienced it as sedating, perhaps through its α_1-adrenoceptor antagonist properties.[19] Another possibility is that improvement in sleep continuity could be due to the 5-HT_2 receptor antagonist properties of risperidone. All but 1 of the patients were taking antidepressant medications with prominent 5-HT reuptake blocking properties, and these agents are known to produce a degree of sleep disruption speculatively through indirect activation of 5-HT_2 receptors.[24] Finally, the effect of risperidone to decrease wake in the patients could be attributable to a resolution of the depressive disorder. This hypothesis is supported by the significant correlation between change in wake and reductions in clinical depression rating. Impaired sleep efficiency is a cardinal symptom of depression, and after risperidone treatment, sleep efficiency had returned to control values.

Conclusions about the possible utility of risperidone augmentation in medication-resistant depression must be tempered by the open-label design of our study. In addition, the patients had a low degree of treatment resistance according to the staging criteria of Thase and Rush[25] in that the majority had been nonresponders to a single antidepressant trial. However, the effect of risperidone on the polysomnogram is consistent with an antidepressant profile. In addition, the fact that improvement in depression correlated with changes in the polysomnogram suggests that the effects of risperidone on sleep architecture (or the pharmacologic mechanisms that regulate it) may be relevant to any antidepressant effects it possesses. Further randomized investigations will be needed to assess whether risperidone may have value as an adjunct in the treatment of depression.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal), venlafaxine (Effexor).

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