Effects of typical antipsychotic drugs and risperidone on the quality of sleep in patients with schizophrenia: a pilot study

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Objective: To investigate the effects of a newer antipsychotic drug, risperidone (a potent serotonin 5-$HT_{2A/2C}$- and dopamine D_2-receptor blocker), on the quantity and quality of sleep in patients with schizophrenia. **Design**: Prospective pilot study. **Setting**: Outpatient treatment at a mental health hospital. **Patients**: Two groups of age- and sex-matched patients with schizophrenia receiving either risperidone (n = 8) or a typical antipsychotic drug (n = 8), and a group of age- and sex-matched controls (n = 8). **Outcome measures:** Sleep quality, measured by a visual analogue scale, and sleep continuity, measured using a movement index calculated from actigraph data. **Results:** Patients with schizophrenia had more disturbed sleep than controls. Compared with patients treated with typical antipsychotic drugs, patients treated with risperidone reported significantly better sleep quantity and quality as well as general functioning. **Conclusion:** Improvement by risperidone may be related to 5-$HT_{2A/2C}$ receptor blockade; however, further controlled studies are required to confirm these results.

Objectif : Étudier les effets d'un nouveau médicament antipsychotique, la rispéridone (puissant bloqueur de la sérotonine 5-$HT_{2A/2C}$ et des récepteurs de la dopamine D_2) sur l'importance et la qualité du sommeil chez les patients atteints de schizophrénie. **Conception :** Étude pilote prospective. **Contexte :** Service de traitement externe d'un hôpital psychiatrique. **Patients :** Deux groupes de patients atteints de schizophrénie et jumelés selon l'âge et le sexe qui prenaient de la rispéridone (n = 8) ou un antipsychotique typique (n = 8), et un groupe de sujets témoins (n = 8) jumelés selon l'âge et le sexe. **Mesures de résultats :** Qualité du sommeil, mesurée sur une échelle analogique visuelle, et continuité du sommeil, mesurée au moyen d'un indice du mouvement calculé à partir de données «actigraph». **Résultats :** Les patients atteints de schizophrénie avaient un sommeil plus troublé que les sujets témoins. Comparativement aux patients traités au moyen d'antipsychotiques typiques, les patients traités à la rispéridone ont déclaré avoir un sommeil de loin meilleur sur les plans quantitatif et qualitatif et mieux fonctionner sur le plan général. **Conclusion :** L'amélioration causée par la rispéridone peut être liée au blocage des récepteurs 5-$HT_{2A/2C}$; d'autres études contrôlées s'imposent toutefois pour confirmer ces résultats.

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Introduction

There is evidence that more than 90% of patients with schizophrenia have sleep problems. Sleep problems may exacerbate existing psychopathology by causing distress and other negative effects on psychosocial rehabilitation and general functioning. It was first speculated that abnormalities in the sleep patterns of patients with schizophrenia were due to the fact that psychosis and dreaming seem to have similar properties.[1] This hypothesis was originally rejected, since early polygraphic studies did not detect gross abnormalities in the sleep patterns of patients with schizophrenia. However, since then, it has been suggested that more subtle rapid-eye movement (REM) sleep abnormalities, such as REM latency and lack of REM rebound after sleep deprivation as well as slow-wave sleep, may be abnormal in patients with schizophrenia.[2-4]

In addition to REM sleep and latency abnormalities in patients with schizophrenia, decrements in slow-wave sleep in about 40% of patients, particularly in the first sleep cycle, have been documented.[4-6] In several of these studies, patients were categorized as not being treated with antipsychotic drugs (APDs), even though they had been medication-free for only a short period of time. This prompts the question of whether these slow-wave sleep and REM changes reflect prior drug treatment or are a part of the pathophysiology of the disorder. Thus, we set out to examine the effects of APDs on the sleep patterns of patients with schizophrenia.

It has been suggested that the effects of atypical and typical APDs on sleep are significantly different.[1,7-9] This difference would be expected, due to variability in the pharmacodynamic profile of APDs. It is well known that the classic typical APDs improve sleep continuity in patients with schizophrenia by increasing total sleep time and improving sleep efficiency.[7,8,10] In comparison with typical APDs, the atypical APDs have a wider therapeutic index and lack extrapyramidal side effects at clinically effective dosages.[11] Examples of the atypical APDs include clozapine, and more recently remoxipride and risperidone. Patients with schizophrenia that are treated with risperidone, a potent dopamine D_2- and serotonin 5-$HT_{2A/2C}$-receptor antagonist introduced in 1993,[12] appear to sleep and function significantly better than patients treated with typical APDs. This appears to be due to the unique action of risperidone on the 5-$HT_{2A/2C}$ receptors; recent evidence suggests that blocking the 5-$HT_{2A/2C}$ receptors is likely to improve both sleep quality and continuity.[13]

To date, there are few studies on the effects of risperidone on sleep. Therefore, we investigated the effects of risperidone on the quality and continuity of sleep in patients with chronic schizophrenia. The results were compared with age- and sex-matched healthy controls and with age- and sex-matched patients with schizophrenia who were treated with typical APDs.

Methods

Subjects

Outpatients attending Leicestershire Mental Health Hospitals who provided informed consent were included in this study. To be included, patients must have had a diagnosis of schizophrenia consistent with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria, and a duration of illness since first diagnosis of at least 2 years. Before starting the study, all patients had received a minimum of 20 weeks of treatment with the same APD that they received during the study. Exclusion criteria for patients included long-term use of any medication or drug that could affect plasma 5-HT concentrations at least 3 months before study enrolment (e.g., anxiolytics, antidepressants, mood stabilizers, addictive drugs [i.e., amphetamines, cocaine, opiates, cannabis, lysergic acid diethylamide and phencyclidine]); chronic alcoholism; clinically evident central nervous system (CNS) infections; cancer; and any medical disorder that may cause sleep abnormalities. Patients were not allowed to receive any additional psychotropic drug (sedative or hypnotic) for at least 5 days before sleep assessment, but they were permitted to continue a single daily dose of procyclidine (5 mg), an anticholinergic drug, as needed.

Patients were assigned to 1 of 2 groups: the risperidone-treated group or the typical APD-treated group. Each group consisted of 4 men and 4 women. All patients were treatment-responsive, psychopathologically stable and had minimal residual psychotic features. Levels of general functioning were rated using the Global Assessment Scale (GAS; 1 to 100).[14]

The control group consisted of 4 men and 4 women. Control subjects were in good physical health, and a medical and neuropsychiatric evaluation of each subject's history indicated that all measures were within normal range. Exclusion criteria included any current use of alcohol or drugs, history of alcohol or drug

abuse, any form of sleep disturbance and current use of psychotropic drugs.

Assessments of the quality and continuity of sleep

The quality of sleep and treatment efficacy were assessed using a 10-cm visual analogue scale (VAS).[15] On the morning following each study night, subjects used the VAS to rate sleep quality ("worst possible" to "best ever": 0 to 10) and morning sleepiness ("awfully sleepy" to "marvellously alert": 0 to 10). Although some studies have not found VAS estimates to be consistent with measurements of sleep microstructure,[15–17] VAS estimates have been reported to be consistent with performance.[18,19]

Continuity of sleep was evaluated using a continuous activity monitoring system.[20] An "actigraph" (a wrist-worn, watch-size activity monitor) was placed on the subject's right wrist at bedtime in their home, and worn for 5 consecutive nights. This provided indirect quantitative information about the timing and continuity of sleep. Handedness was not evaluated, since we and others[21,22] have demonstrated that left- and right-wrist recordings provide equivalent results. Actigraph data were transferred to a computer by means of a monitor interface and analyzed by Actplan and Actstat software packages (Switzerland). A movement index (MI) was calculated by dividing the total number of points with movement by the total number of points recorded, and expressed as a percentage.[21]

Results

Patients in the risperidone-treated group had a mean age of 36.1 (standard deviation [SD] 9.2) years, with a mean duration of illness of 109 months and a mean age at onset of 24.3 (SD 8.1) years. This treatment group received a mean dose of 9.5 (SD 4.3) mg per day of risperidone for 42.5 (SD 16.8) weeks. Patients in the typical APD-treated group had a mean age of 35.4 (SD 11.5) years, with a mean duration of illness of 103 months and a mean age at onset of 23 (SD 7.5) years. This treatment group received either chlorpromazine, haloperidol or flupenthixol at a mean dose of 606.3 (SD 309) mg per day (chlorpromazine equivalent) for 191.3 (SD 62.7) weeks. Control subjects had a mean age of 33.8 (SD 11.6) years.

The 2 treatment groups and the control group did not differ significantly in mean age. Furthermore, the 2 treatment groups did not significantly differ in their duration of illness or their age at onset. However, the 2 treatment groups did significantly differ in their duration of treatment (Student's t-test, $p < 0.05$), with the typical APD-treated group having been treated with the typical APD for 91.3 (SD 62.7) weeks and the risperidone-treated group having been treated with risperidone for 9.5 (SD 4.3) weeks. In terms of functioning, the GAS scores of the 2 treatment groups did differ significantly (Student's t-test, $p < 0.05$), with the typical APD-treated group reporting significantly lower levels of functioning (mean GAS score = 33.2 [SD 15.8]) than the risperidone-treated group (mean GAS = 61.2 [SD 17.2]).

When compared with controls, patients treated with typical APDs reported significantly lower sleep quality (mean VAS score of 7.5 [SD 2.2] versus 3.4 [SD 2.6]) and morning sleepiness (mean VAS score of 7.6 [SD 1.6] v. 3.5 [SD 2.4]), and had significantly higher MI (mean MI of 3.6 [SD 2.2] v. 20.7 [SD 9.6]). When compared with controls, patients treated with risperidone did not differ significantly in reports of sleep quality (mean VAS of 7.5 [SD 2.2] v. 6.7 [SD1.5]) and morning sleepiness (mean VAS of 7.6 [SD 1.6] v. 6.5 [SD 2.6]), but did have significantly higher MIs (mean MI of 3.6 [SD 2.2] v. 11 [SD 5.7]). These results are presented in Fig. 1.

In terms of different APD treatment effects (Fig. 1), risperidone-treated patients scored significantly better when compared with typical APD-treated patients in terms of sleep quality (mean VAS of 6.7 [SD 1.5] v. 3.4 [SD 2.6]) and morning sleepiness (mean VAS of 6.5 [SD 2.6] v. 3.5 [SD 2.4]). In addition, risperidone-treated patients had significantly better MIs (mean MI of 11 [SD 1.7] v. 20.7 [SD 9.6]).

Discussion

Our results demonstrated that, when compared with healthy control subjects, patients with schizophrenia have significantly more sleep abnormalities, as assessed by their reports of quality of sleep and morning sleepiness. Their MIs, as assessed by actigraphy, were consistent with this finding. However, patients treated with risperidone appear to have significantly improved sleep quality, morning alertness and lower MIs as well as improved daily functioning when compared with patients treated with typical APDs.

Our results are consistent with the findings of other studies,[23,24] which report that individuals with schizophrenia have more sleep abnormalities compared with healthy control subjects. To our knowledge, there are no

human studies, and only 1 animal study, that has indirectly measured the effect of risperidone on sleep. Dugovic et al[25] reported that rats given low dosages of risperidone demonstrated a significant increase in deep slow-wave sleep, yet high dosages of risperidone were associated with a significant decrease in wakefulness and light slow-wave sleep.

In humans, it is hypothesized that risperidone would affect slow-wave sleep, since slow-wave sleep is primarily regulated by 5-HT_2 receptors[25,26] and risperidone is a potent D_2- and 5-$HT_{2A/2C}$-receptor antagonist.[11] The effect of risperidone on the quality of sleep has been reported in some studies that examined its efficacy and safety. For example, in a study evaluating the use of risperidone in the treatment of affective illness and obsessive–compulsive disorder, Jacobsen[27] reported an improved quality of sleep following treatment with risperidone for acute and chronic psychosis accompanying affective illness. In contrast, in a study comparing the side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia, Daniel et al[9] reported that patients taking risperidone complained of more insomnia and patients on clozapine complained of more sedation.

Interpretation of the data is limited due to the absence of polysomnographic measures and detailed actigraph parameters (such as sleep latency), which have been correlated with sleep performance. In addition, MI provides only indirect data. Finally, the small number of subjects, the nonrandom allocation to treatment groups and the possible effect of extrapyramidal side effects on the MI score, could all have affected the interpretation of this study.

Conclusion

Our findings of improved sleep continuity and general

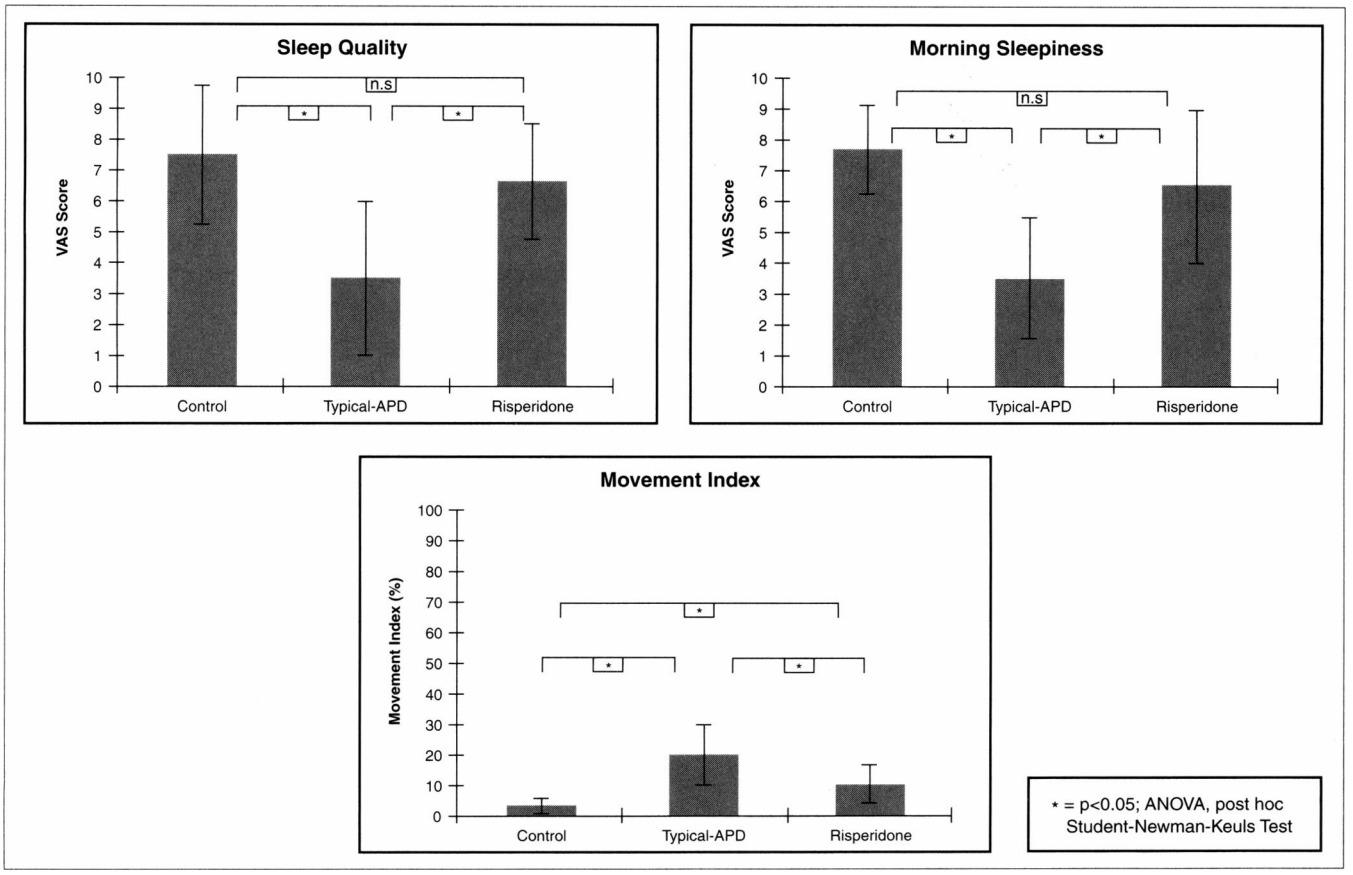

Fig. 1: Mean and standard deviation (error bars) for sleep quality, morning sleepiness and movement index in groups of patients with schizophrenia taking a typical antipsychotic drug (APD) or risperidone, and in a group of healthy controls. Sleep quality and morning sleepiness were rated on a visual analogue scale (VAS) of 10 points. The movement index was calculated from wrist-worn, watch-size activity monitors (actigraphs) worn during sleep, and is equal to the total number of points with movement divided by the total number of points recorded.

functioning for risperidone-treated patients, but not for patients treated with typical antipsychotic drugs, suggests that the unique action of risperidone at the 5-$HT_{2A/2C}$ receptors may enhance sleep. Risperidone may also be particularly useful as an antipsychotic drug for the treatment of patients with schizophrenia who experience sleep disturbances. Further controlled double-blind studies are required to confirm these findings.

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