Lack of Effects of Pramipexole on REM Sleep Behavior Disorder in Parkinson Disease

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Study Objectives: REM sleep behavior disorder (RBD) is a common manifestation of Parkinson disease (PD) which is characterized by dream-enacting behaviors, unpleasant dreams, and loss of muscle atonia during REM sleep. Dopaminergic mechanisms are thought to play a role in RBD pathogenesis. To further asses such a role, we have evaluated the effect of pramipexole, a dopamine receptor agonist, on RBD features in PD patients.

Setting: University hospital sleep disorder center.

Participants: Eleven PD patients with untreated RBD.

Interventions: Not applicable.

Measurements and results: In a prospective study, 11 consecutive PD patients with untreated RBD on levodopa monotherapy were placed on pramipexole to further ameliorate their parkinsonism. The effects on RBD were evaluated before and 3 months after stable pramipexole therapy through patient and bed partner interviews and blind assessment of video-polysomnographic measures. Pramipexole improved parkinsonism in all patients. Patients and bed partners reported no significant changes in frequency and severity of the abnormal RBD related motor and vocal sleep behaviors or the frequency of unpleasant dreams. Video-polysomnography analyses showed no differences in RBD related sleep measures including tonic submental electromyographic activity, phasic submental electromyographic activity, percentage of REM sleep time spent with abnormal behaviors, and severity of the abnormal behaviors detected on the videotapes.

Conclusion: In PD, pramipexole improved parkinsonism but did not modify RBD related symptoms and objective video-polysomnographic abnormalities. This observation suggests that in PD, dopamine mechanisms do not play a central role in the pathogenesis of RBD.

Keywords: REM sleep behavior disorder, Parkinson disease, pramipexole, dopamine

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PARKINSON DISEASE (PD) IS A NEURODEGENERATIVE DISORDER ASSOCIATED WITH LOSS OF THE DOPAMINERGIC CELLS IN THE SUBSTANTIA NIGRA resulting in bradykinesia, tremor, and rigidity. These classical motor symptoms are responsive to dopaminergic agents. In PD, the degenerative process also involves non-dopaminergic neuronal areas beyond the substantia nigra such as the lower brainstem, the amygdala, and the cortex. Impairment of these brain areas in PD account for the occurrence of several non-motor symptoms, including dysautonomia and dementia, which do not respond to dopamine replacement therapy.[1]

REM sleep behavior disorder (RBD) is a frequent feature of PD that is characterized by dream-enacting behaviors, unpleasant dreams, and loss of muscle atonia during REM sleep.[2,3] It is unknown if RBD in PD results from dopaminergic deficiency. To assess whether dopaminergic dysfunction plays a major role in the pathogenesis of RBD in PD, we prospectively examined the therapeutic effect of pramipexole, a D_2-D_3 dopamine receptor agonist, on RBD features in patients with PD.

PATIENTS AND METHODS

Patient Selection

All PD patients participating in a prospective study evaluating the effect of pramipexole on somnolence and showing RBD in baseline video-polysomnography (VPSG) were studied. At the time of study initiation, all subjects were on stable levodopa monotherapy and were started on pramipexole as an adjunct dopaminergic treatment to further improve their motor function.[4,5] Exclusion criteria were dementia, hallucinations, psychosis, current or previous treatment with a dopamine agonist, antidopaminergic agents, or clonazepam, and an apnea-hypopnea index >10 on VPSG.[6] None of the patients had received treatment for RBD. Pramipexole was started at 0.54 mg daily divided in 3 doses, and the last dose was given one hour before bedtime. During this study, levodopa dosage was not modified, and pramipexole dose was increased gradually according to parkinsonism response and tolerance. Evaluations in this study were done at baseline (within the week before initiation of pramipexole therapy) and 3 months after optimal stable dose of pramipexole was reached. All patients gave informed written consent, and the study was approved by the ethics committee at our institution.

Parkinsonism Evaluation

Diagnosis of PD was made according to UK Brain Bank Criteria.[7] Parkinsonism was assessed using the motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS-III)[8] and

Table 1—Sleep Variables Before and After 3 Months of Stable Pramipexole Treatment

	Baseline	Pramipexole	P value
Sleep efficiency (%)	76.0 ± 10.3	85.0 ± 6.5	0.09
Total sleep time (min)	367.6 ± 55.7	418.2 ± 32.3	0.05
Stage 1 (%)	22.1 ± 17.7	22.3 ± 15.0	0.90
Stage 2 (%)	46.8 ± 15.2	51.8 ± 11.9	0.59
Stage 3-4 (%)	11.9 ± 8.0	12.5 ± 9.1	0.70
Stage REM (%)	19.2 ± 7.3	13.4 ± 5.5	0.18
REM sleep latency (%)	157.2 ±122.4	152.3 ± 72.7	1.00
REM sleep episodes (n)	4.8 ± 1.4	4.5 ± 1.8	0.88
REM sleep time with abnormal behaviors (%)	9.8 ± 8.6	7.6 ± 6.0	0.59
REM density (%)	15.1 ± 5.3	13.6 ± 6.4	0.53
Submental phasic electromyographic activity (%)	16.8 ± 14.6	11.9 ± 9.4	0.37
Submental tonic electromyographic activity (%)	31.2 ± 35.8	28.0 ± 37.4	0.51
PLMS index (n)	13.2 ± 27.1	0 ± 0	0.10

Hoehn and Yahr staging.[9] Activities of daily living were evaluated with the Schwab and England disability scale.[10] These evaluations were performed one hour after the morning dose of levodopa at baseline, and one hour after the morning dose of levodopa plus pramipexole after 3 months of stable pramipexole treatment.

Sleep Evaluation

Diagnosis of RBD required a history of long-standing dream-enacting behavior and VPSG evidence of REM sleep increased tonic and/or phasic electromyographic activity associated with abnormal behaviors.[2] To assess the effect of pramipexole on RBD symptoms, we studied only patients who were aware of their abnormal sleep behaviors and had a bed partner who could substantiate the patient's report and provide additional information. Patients and bed partners were asked to assess if the frequency and severity of the RBD motor and vocal behaviors improved, did not change, or worsened after the introduction of pramipexole. Patients were also instructed to score the frequency of their unpleasant dreams according to question 5.h of the Pittsburgh Sleep Quality Index as 0 (not during the past month), 1 (less than once a week), 2 (once or twice a week), and 3 (≥ 3 times a week).[11]

Patients underwent time-synchronized VPSG studies during 2 consecutive nights, both at baseline and 3 months after optimal stable dose of pramipexole. The first night was regarded as the night for adaptation, and the second night measures were used for analyses. All quantitative VPSG analyses were conducted by scorers blinded to the treatment condition. Sleep stages were scored according to standard criteria,[12] with allowance for REM sleep without atonia. During REM sleep we calculated the REM density and the phasic and tonic electromyographic activity in the submentalis muscle as previously reported.[13] Percentage of abnormal behaviors in REM sleep was calculated as the total REM sleep time divided by the time spent in REM sleep containing motor and vocal behaviors detected on the videotapes. Severity of the abnormal behaviors observed on the videotapes during REM sleep was classified as mild, moderate, and severe, as previously reported.[14] Periodic leg movements in sleep (PLMS) were scored following the Atlas and Scoring Rules by the Atlas Task Force of the American Sleep Disorders Association,[15] and the PLMS index (number of periodic leg movements per hour of sleep) was calculated.

Statistical Analysis

Changes in parkinsonism and polysomnographic variables before and after pramipexole treatment were assessed with the Wilcoxon signed rank test. Unpleasant dream frequency before and after pramipexole therapy was analyzed, and differences between groups (groups 0, 1, 2, and 3, according to question 5 h of the Pittsburgh Sleep Quality Index) were evaluated using the chi-squared test.

RESULTS

Patients were 8 men and 3 women with a mean age of 62.1 ± 8.0 years, a mean age of parkinsonism onset of 54.9 ± 10.7 years, and a mean parkinsonism duration of 7.2 ± 4.8 years. At study entrance, the mean levodopa daily dose was 562.5 ± 334.1 mg and the mean levodopa treatment duration was 6.5 ± 4.6 years. Age of RBD onset was 58.2 ± 9.1 years and the mean RBD duration was 3.9 ± 2.8 years. RBD developed after parkinsonism in 6 patients, occurred simultaneously in 2, and preceded the onset of parkinsonism in the remaining 3. At the end of the study, pramipexole daily dose was 2.10 mg in all patients, and no major adverse effects were reported.

Parkinsonism Evaluation

Parkinsonism improved in all patients after the introduction of pramipexole. The mean UPDRS-III score decreased from 17.09 ± 4.57 to 9.27 ± 5.04 points (P = 0.003), the mean Hoehn and Yahr stage changed from 1.86 ± 0.39 to 1.55 ± 0.49 (P = 0.063), and the Schwab and England disability scale improved from 85.45 ± 5.2 to 95.45 ± 5.20 (P = 0.005).

Sleep Evaluation

No changes in frequency and severity of motor and vocal RBD symptoms were reported either by patients or by bed partners after stable pramipexole therapy. Complex and intense RBD behaviors (e.g., semipurposeful behaviors, waving the

arms vigorously, kicking) persisted despite the introduction of pramipexole. Patients experienced a reduction in the frequency of unpleasant dream recall, but differences between groups were not significant. At baseline, 4 patients did not recall unpleasant dreams, 2 recalled unpleasant dreams less than once a week, 3 patients once or twice a week, and 2 recalled unpleasant dreams ≥ 3 times a week. After 3 months of stable pramipexole therapy, 5 patients reported no unpleasant dreams, 5 patients recalled unpleasant dreams less than once a week, and one patient recalled unpleasant dreams ≥ 3 times a week.

The main VPSG findings before and after pramipexole treatment are presented in the Table 1. There were no differences in RBD related sleep measures including tonic submental electromyographic activity, phasic submental electromyographic activity, and percentage of REM sleep time spent with abnormal behaviors. At baseline, abnormal behaviors severity on videotapes was mild in 5 subjects, moderate in 4, and severe in 2. After pramipexole therapy, severity did not change in 9 subjects and increased in 3 (from mild to moderate in 2, and from moderate to severe in one). At baseline, 3 patients had a PLMS index greater than 10 (29, 30, and 87). After pramipexole therapy, PLMS were not detected in any patient.

DISCUSSION

In this study, pramipexole improved parkinsonism but did not produce changes in RBD symptoms and objective VPSG parameters. Given that pramipexole is a D_2-D_3 dopamine agonist with a half-life of 8-12 hours,[5] which in our study was given at bedtime for 3 months, our findings do not support a significant central nervous system dopaminergic role in the pathogenesis of RBD in PD.

Previous published reports in subjects with PD have shown conflicting data regarding the effect of dopaminergic agents on RBD. Although some PD patients experienced subjective improvement of RBD symptoms after the administration of levodopa[16] and pramipexole,[17] others reported that RBD onset was temporarily associated with the initiation of levodopa,[18] dopamine agonists,[19] and selegiline.[20] Several lines of evidence are in agreement with our findings suggesting that in PD, dopaminergic impairment is not the major substrate for RBD pathogenesis. PD patients, for example, commonly develop RBD during long-term effective dopaminergic treatment for parkinsonism.[21] Also, total levodopa equivalent dose and the use of dopamine agonists is not different between PD patients with and without RBD;[22-24] and in PD patients with RBD, total levodopa equivalent dose is not related to measures of RBD severity.[21] In addition, surgical techniques in PD that provide effective control of responsive dopaminergic motor symptoms do not ameliorate RBD.[25,26] The finding that parkinsonism disappears during RBD-related motor and vocal behaviors led to the hypothesis that the abnormal movements in REM sleep are generated in the motor cortex following the pyramidal tract bypassing the dopaminergic basal ganglia circuits.[25,27] Finally, although not systematically studied, there are no published reports of RBD precipitated by antidopaminergic medications or occurring in subjects with drug-induced parkinsonism.

One study showed that in RBD patients with multiple system atrophy, REM sleep tonic, but not phasic, electromyographic activity was inversely correlated to monoaminergic binding in the striatum.[28] In contrast, it has been shown that administration of dopaminergic agents in subjects with idiopathic RBD[29] and RBD related to PD[18] increases the tonic, but not phasic, electromyographic activity during REM sleep. It should be noted that excessive phasic, but not tonic, electromyographic activity in REM sleep is thought to reflect the clinical behavioral manifestations of RBD.[2,28]

Our findings seem to be in contrast to what has been reported in idiopathic RBD, a condition in which pramipexole appears to improve RBD in some patients,[17,29] and striatal dopamine transporters may be reduced.[30] The evidence supporting the effectiveness of pramipexole in idiopathic RBD, though, is not compelling since post-treatment VPSG studies demonstrate worsening or no improvement of REM sleep electromyographic abnormalities[29] or have not been performed.[30,31] It cannot be excluded, however, that despite clinical and VPSG similarities in RBD features,[21] idiopathic RBD and RBD in PD may be 2 different stages of the same condition or 2 different conditions.

We acknowledge the limitations of our study, namely its open nature, lack of a control group, and the small number of patients. The results of our study, though, were based on subjective reports of patients and bed partners, indicating that the frequency and severity of dream-enacting behaviors did not change during pramipexole therapy, and a blind quantitative objective VPSG analysis, which demonstrated no changes in muscular activity and abnormal behaviors during REM sleep after pramipexole therapy. A validated rating scale of RBD related clinical symptomatology is lacking and needs to be defined. Based on the published available data[18-27] and our findings, we believe that in PD, pramipexole does not alter RBD and that impairment of dopaminergic striatal mechanisms does not play a key role in the pathogenesis of this parasomnia. It cannot be excluded, however, that dopaminergic mechanisms play some role in the genesis of RBD, but once RBD has become clinically established, other neurotransmitters become operational in the ongoing pathophysiology. In the setting of PD, it seems appropriate to consider RBD as another non-dopaminergic manifestation and not to treat this parasomnia with dopaminergic agents.

DISCLOSURE STATEMENT

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