Pramipexole in the Management of Restless Legs Syndrome: An Extended Study

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Study Objectives: To determine whether pramipexole used over an extended time for restless legs syndrome (RLS) remains effective; whether the dose of the drug needs to be increased; whether augmentation develops; and whether side effects, especially sleepiness, are prominent.

Design: Retrospective review of the records of consecutive patients treated with pramipexole for RLS.

Setting: Sleep disorders center in an academic hospital.

Patients: 60 consecutive patients treated with pramipexole for RLS.

Interventions: N/A

Measurements and Results: Pramipexole was completely effective in controlling RLS in 67%, partially effective in 27%, and ineffective in 7% of patients. Eleven patients (18%) discontinued pramipexole after less than 4 months; the remainder were followed for a mean of 27.2 months, during which only 4 others stopped the drug. The median daily dose increased from 0.38 mg after stabilization to 0.63 mg at the end of the study. Forty percent experienced mild side effects, most commonly insomnia, nausea or dyspepsia, and dizziness. Only 5% experienced sleepiness, and none experienced sleep attacks while driving. Augmentation developed in 33%, most in the first year and all by 30 months. Augmentation was not predictable by prior augmentation with other dopaminergic agents. Only 1 patient discontinued pramipexole because of augmentation.

Conclusions: Pramipexole was effective for RLS with continued response with time. Modest escalations in dose occurred, partly due to additional doses prescribed for augmentation. Side effects were common, but generally mild and tolerated. Sleepiness while driving was not a problem. Augmentation occurred in 33% of patients but was treatable with increased doses earlier in the day.

Key Words: restless legs syndrome, pramipexole, augmentation

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INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) IS CHARACTERIZED BY AN URGE TO MOVE THE LEGS, USUALLY ASSOCIATED WITH UNCOMFORTABLE SENSATIONS, OCCURRING AT REST, RELIEVED BY MOVEMENT, AND MOST SEVERE IN THE EVENING OR NIGHT.1 Restless legs syndrome is a common disorder, with an estimated prevalence of 10% in the United States.2 It responds to dopaminergic therapies, including both levodopa and dopamine-receptor agonists.3 Levodopa treatment is associated with a high frequency of daytime augmentation, in which the symptoms worsen earlier in the day after administration of the drug in the evening.4 Thus the dopamine-receptor agonists, including pergolide, pramipexole, and ropinirole, have become widely used. A small number of controlled trials5-14 have confirmed their efficacy, but few extended follow-up studies5-14 have been reported. No valid comparisons of the different dopamine-receptor agonists have been performed.

Pramipexole is a nonergoline dopamine agonist with particular affinity for the D2 receptor.15 It is largely excreted by the kidneys and has a plasma half-life of 8 to 12 hours.16 It is believed to cause fewer side effects than pergolide, especially less nausea. We report here an extended follow-up study of 60 consecutive patients treated with pramipexole for RLS. The goals of the study were to explore whether pramipexole remained effective with time, whether the dose of the drug escalated, whether augmentation developed, and whether side effects, especially sleepiness, affected therapy.

RESULTS

Demographic Data

Sixty patients were identified. Thirty-six were women (60%); 24 men. Restless legs syndrome was familial in 21 patients (35%). All patients complained of insomnia, daytime tiredness, or both due to RLS. The periodic limb movement index was greater than 10 per hour in all 28 patients who underwent polysomnography (range 12-139/hour). The mean age at the commencement of pramipexole therapy was 57.7 years (range, 25-82 years).

METHODS

Mayo Clinic records were reviewed, and all patients fulfilling the following criteria were identified: a diagnosis of RLS (International RLS Study Group criteria)1) made at the Mayo Sleep Disorders Center; treatment with pramipexole initiated between January 1, 1998, and December 31, 1999; and either a minimum of 4 months of follow-up data available or patient known to have discontinued pramipexole within 4 months of initiation. Charts were reviewed, and data abstracted and analyzed. Patients were seen by 1 of 9 sleep specialists, all diplomates of the American Board of Sleep Medicine. However, a single physician (MHS) treated 52% of the patients. Augmentation was defined as the new development or increase in severity, duration, or anatomic distribution of RLS earlier in the day than the time a medication for RLS was taken. Efficacy was judged from the charts by the reviewing physician and graded as completely effective (no residual RLS), partially effective (improvement in RLS, but some RLS still present), and ineffective (no improvement in RLS). Sleepiness was determined by patient report on follow-up visits. Epworth Sleepiness Scales (ESS) were available for some patients but not systematically recorded. Mean values were used as measures of central tendency unless the distribution was skewed, in which cases median values are reported. The study was approved by the Institutional Review Board.

Disclosure Statement

No significant financial interest/other relationship to disclose.

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In all but 2 patients, pramipexole was introduced to replace other medications. Thirty-five patients were using carbidopa/levodopa, 22 pergolide, and 1 clonazepam at the time pramipexole was commenced. Reasons for changing medications were daytime augmentation (carbidopa/levodopa 15, pergolide 5), side effects (carbidopa/levodopa 7, pergolide 10, clonazepam 1), inadequate response (carbidopa/levodopa 11, pergolide 6), and early-morning rebound (carbidopa/levodopa 2). Patients were commenced on either 0.125 or 0.25 mg pramipexole as a single evening dose, with the dose being increased by 0.125 or 0.25 mg every 2 to 3 days until relief was obtained. The previous medication was either discontinued when pramipexole was started or weaned over less than a week.

Follow-Up Data

Pramipexole was completely effective in controlling RLS symptoms in 40 patients (67%), partially effective in 16 (27%), and ineffective in 4 (7%). Twenty-four patients (40%) reported side effects of the medication (see Table 1). Most side effects were mild and transient. None of the 3 patients with excessive daytime sleepiness felt the need to discontinue the medication as a result, and none reported “sleep attacks” while driving. Two of the 3 patients had completed follow-up ESS with scores of 4 and 11.

Eleven patients (18%) discontinued pramipexole less than 4 months after commencement (range 1 week-4 months). Reasons for stopping were side effects in 8 patients, lack of efficacy in 1, and both side effects and lack of efficacy in 2.

The mean duration of follow-up for the remaining 49 patients was 27.2 months (range 4-46 months). After initial stabilization, the median dose required before sleep was 0.38 mg (range, 0.125-2.0 mg). By the end of the study, the median daily dose had increased to 0.63 mg (range, 0.25-4.5 mg). By the end of the study, 14 patients (29%) were taking the drug twice a day, with the first dose usually in the afternoon or early evening. Four patients (8%) required pramipexole 3 times a day, 3 taking it in the morning, afternoon, and before bed, and 1 taking it in the early afternoon, early evening, and before bed. Nineteen patients (39%) had not needed to increase the dose at all. There was no correlation between the final daily dose and the duration of use of pramipexole (r=0.15, P=0.29). Four patients (8%) discontinued pramipexole after more than 4 months (range, 11-26 months) because of side effects (2), lack of efficacy (1), and augmentation (1). Sixteen patients (33%) took 1 or more additional medications for RLS: 13 benzodiazepines, 5 opioids, and 1 gabapentin.

Augmentation developed in 16 of the 49 patients (33%) after a mean of 13.8 months treatment (range, 2-31 months). The mean daily dose when augmentation developed was 0.56 mg (range, 0.25-1.0 mg). A Kaplan-Meier plot indicated that 20% of patients had developed augmentation after 1 year of treatment and 30% after 2 years. The risk of augmentation tapered off after 2.5 years of treatment. Prior augmentation with either carbidopa/levodopa or pergolide was not associated with a significantly increased risk of augmentation with pramipexole (Table 2). Augmentation was generally treated with additional doses earlier in the day and resulted in discontinuation of the drug in only one patient.

DISCUSSION

The results of this consecutive case series suggest that pramipexole remains successful in treating RLS in the majority of patients over a mean follow-up period of 27.2 months. Pramipexole was completely effective in two thirds of the patients and ineffective in only 7%. In the only placebo-controlled trial of pramipexole for RLS, 5 10 patients reported a 72% to 84% reduction in RLS compared to placebo. Seven of these patients participated in a follow-up study13 with a mean duration of 7.8 months and showed sustained responses to the drug at the end of the study. Seventy-five percent of our patients were still taking pramipexole at the end of the study, with 18% discontinuing it in the first 4 months and the remainder between 11 and 26 months. This compares favorably to follow-up data on pergolide treatment of RLS. Three studies have reported that 73% to 79% of 25 to 28 patients were still using pergolide after a mean follow-up period of 14 to 25 months10,12,14.

The median initial dose providing relief from RLS was 0.38 mg. This is similar to previous studies (0.37-0.54 mg).5,11 By the end of the study, the median daily dose had risen to 0.63 mg, and 61% of the patients had increased their initial therapeutic dose. This can be partially accounted for by the addition of doses earlier in the day by patients who had developed RLS augmentation (37%), but it must be assumed that the remaining 24% had developed either some degree of tolerance to the drug or increasing severity of RLS. There was no correlation between the final daily dose and duration of therapy in the group as a whole, indicating that the development of tolerance with time was by no means inevitable.

Our study demonstrates that RLS augmentation definitely occurs with the use of pramipexole, with one third of our patients affected. The risk was highest early after starting treatment, with an augmentation onset rate of about 20% in the first year of treatment and 10% in the second year. After 2.5 years, no previously unaffected patient developed aug-
mendment. The shortest time to augmentation was 2 months. In contrast, Ferini-Strambi found an augmentation rate of only 8% in 60 patients followed for at least 6 months. These discrepant results may be due to the shorter duration of follow-up in their study. Studies of pergolide, however, report augmentation rates with of 15% to 27% after mean treatment period of 14 to 25 months. In general, augmentation with pramipexole was relatively mild, and only 1 patient needed to discontinue the drug as a result. Augmentation could usually be controlled by adding doses of pramipexole earlier in the day, an approach we have previously reported with pergolide. Our data also indicate that prior augmentation with levodopa or pergolide does not predict augmentation with pramipexole and vice versa. Thus replacing 1 dopaminergic agent that has resulted in unacceptable augmentation with another may be a reasonable strategy.

Forty percent of patients noted side effects, which were usually mild, tolerable, and nonpersistent. As this was not a placebo-controlled study, the frequency of side effects directly related to the drug may be overestimated. Eight patients discontinued pramipexole due to side effects within 4 months of starting the drug, and 2 patients discontinued at a later stage. Insomnia, nausea or dyspepsia, and postural lightheadedness were the most common adverse reactions, but none occurred in more than 13% of the patients. This compares to side effects in 60% and 68% of patients taking pergolide for RLS in 2 follow-up studies. Excessive daytime sleepiness occurred in only 5% of our patients and did not result in discontinuation of pramipexole. No patients reported episodes of sleep without prior warning (“sleep attacks”) while driving. The frequency of sleepiness reported may be an underestimation, as standardized questions or instruments such as the ESS were not used systematically. However, Stiasny et al also found only 1 of 24 patients described sleepiness in the evening related to taking a dose of the medication, and none reported “sleep attacks.” The risk of sleepiness with pramipexole, especially while driving, appears to be lower in patients with RLS than in patients with Parkinson disease, possibly due to differences in the dose and timing of medication.

We acknowledge certain limitations of our study. First, our study was retrospective, but detailed notes had been kept on all patients, allowing data to be easily abstracted. The different sleep specialists may have variably interpreted patients’ responses, but all work together in the same academic practice and more than half the patients were followed by a single physician. However, a prospective study would be ideal in more accurately determining the long-term benefits and risks of the medication. Second, we did not use quantitative instruments to measure efficacy, augmentation, or adverse reactions, but an RLS severity scale has only recently been validated, and no validated scales to measure augmentation are yet available. Third, all but 2 of our patients were prescribed pramipexole because of problems with other RLS medications, so our sample is biased toward patients with less easily treatable disease. It is also possible that the prior use of a different dopamine agonist might have affected the patients’ responses to pramipexole. Also, one third of our patients were taking additional medications for RLS, predominantly benzodiazepines. Nevertheless, our findings that pramipexole is well tolerated and effective over a mean of more than 2 years in this more-complex patient group leads us to predict that even better outcomes may be achievable with patients treated de novo with this drug.

REFERENCES