Cabergoline is an Effective Single-drug Treatment for Restless Legs Syndrome: Clinical and Actigraphic Evaluation

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Study Objectives: To evaluate the efficacy and the safety of cabergoline, a dopamine-receptor agonist with a long half-life, in restless legs syndrome (RLS).

Design: A 2 month, single blind, open labeled clinical trial. Patients were evaluated with polysomnography at baseline (B), following 1 week of placebo (T0), and after 1 week (T1) and 2 months (T2) of cabergoline treatment. The clinical global impression was assessed using International RLS Study Group Rating Scale and nocturnal actigraphy.

Setting: Sleep Disorders Center.

Patients: Twelve patients with moderate to severe RLS (mean age 56.6 years) who were naive to treatment with dopaminergic agents.

Interventions: Upward titration of cabergoline (from 0.5 mg to 2 mg) in a single evening dose.

Measurements and Results: Ten patients completed the study (mean dose, 1.1 mg), and all showed an improvement of RLS symptoms. The results from the International RLS Study Group Rating Scale showed similarities between B (24.3±2.9) and T0 (23.1±5.9; P=0.6), with significant improvement at T1 (12.5±6.0; P=0.01 vs B and T0) and T2 (9.8±6.9; P=0.001 vs B and P=0.005 vs T0). The mean nocturnal activity value measured by actigraphy during week 1 decreased from T0 (19.8±9.3) to T1 (13.6±6.4) and dropped significantly at T2 (8.5±5.3; P=0.05). Nine patients continued the treatment up to 12 months with consistent efficacy, few side effects, and no augmentation.

Conclusions: Low doses of cabergoline showed effectiveness and safety in patients with moderate to severe RLS, with no appearance of augmentation phenomenon. Double blind, crossover, polysomnographic studies are necessary to confirm this preliminary data.

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INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) IS CHARACTERIZED BY 1) AN INTENSE AND IRRESISTIBLE URGE TO MOVE THE LEGS, USUALLY ASSOCIATED WITH SENSORY COMPLAINTS; 2) MOTOR RESTLESSNESS; 3) WORSENING OF THE SYMPTOMS AT REST AND RELIEF WITH MOVEMENT; AND 4) INCREASE IN SEVERITY OR EXCLUSIVE APPEARANCE IN THE EVENING OR AT NIGHT.1 Restless legs syndrome is a sensorimotor disorder that may have a profound impact on sleep, leading to difficulties in falling asleep and in maintaining sleep, with a prevalence in Western countries ranging between 4 to 10% of the general population. Approximately 15% of all people with RLS are thought a severe enough form of the disorder that they would seek treatment; therefore, appropriate candidates for drug treatment for RLS comprise between 1 to 2% of the general population.2 The diagnosis for RLS is clinical (based upon the patient’s history and the International RLS Study Group [IRLSSG] criteria); the diagnosis of periodic limb movements of sleep (PLMS), a periodic motor phenomenon of the legs that affects as many as 80-90% of people with RLS, requires polysomnographic recording.3

Various agents have been used to treat RLS; however, a recent review and practice guidelines by the American Academy of Sleep Medicine claims that dopaminergic agents (DAs) are the most successful drugs for RLS treatment.4 The first DA to be used to treat RLS, and the most effective, is L-dopa as regular and sustained-release compounds; however, this drug has a high incidence of side effects including rebound and augmentation.5 The rebound phenomenon is defined as an end-of-dose response with RLS symptoms typically occurring in the morning hours, immediately after awakening;6 augmentation, on the other hand, is the earlier onset of RLS symptoms in the evening (compared to the onset before treatment), with possible appearance of symptoms during the day, an involvement of other parts of the body (i.e. the arms), and an increase in severity.6 It is possible that these phenomena, and in particular augmentation, may be due to the short duration of action (1-2 hours) of L-dopa, but they have been described with the use of other DAs such as pergolide (half-life, of 7-16 hours) and pramipexole (half-life, 8-12 hours), although to a lesser degree and with a lower severity.7,8 This suggests that augmentation may be related to factors other than the severity of RLS or the high dosages of DAs but, rather, to the duration of action of the drug. Therefore, identifying alternative treatments options such as longer-acting dopamine agonists is of interest, particularly for patients with moderate to severe forms of RLS. Cabergoline, a D1/D2 receptor agonist with a half-life of more than 65 hours, may be an appropriate choice in the treatment of RLS. This compound has shown efficacy in patients with severe and resistant RLS at low doses (0.5-2 mg); in one study,9 patients who experienced augmentation with L-dopa therapy obtained relief from the augmentation with the use of cabergoline as an add-on treatment.

Therefore, we aimed to evaluate the effectiveness and the safety of cabergoline in RLS patients who have never received DAs as treatment in a single-blind, open-label, clinical trial, in which the patients were evaluated by means of the IRLSSG Rating Scale,10 and by nocturnal monitoring of leg activity (with an actigraph worn at the ankle).

PATIENTS AND METHODS

Twelve patients (4 women, 8 men) with idiopathic RLS, diagnosed according to the IRLSSG criteria,1 enrolled in the study. The mean age was 56.6 years (range, 38-73), and the mean age at RLS symptom onset was 39.3 years (range 20-56 years). All patients had been previously treated with benzodiazepines (1 with benzodiazepines and opioids) but none had ever used DAs, and all refrained from using any drugs for at least 3 weeks before the study began.
All patients underwent neurologic examination, electromyography and nerve conduction studies of the lower limbs, laboratory examinations including serum ferritin and iron levels, and 1 night of polysomnography to exclude other pathologies (such as sleep apnea) and to confirm the presence of PLMS. All patients also completed the IRLSSG Rating Scale at baseline (B), after 1 week of placebo (T0), and after 1 week (T1) and 2 months (T2) of treatment with cabergoline. The physician completed a Clinical Global Impression (CGI) scale for each patient at the same time intervals. Nocturnal activity was evaluated, by means of an actigraphic recorder (Motion Logger, Ambulatory Monitoring, Ardsley, NY) worn at the ankle. Mean activity value during the night correlates with PLMS scoring but it is not considered to be fully specific in identifying PLMS—generally it underestimates in respect to polysomnography, using both manual and automatic analysis.11-13 Nevertheless, this simple device may be useful to follow the PLMS of patients with RLS who are receiving treatment and may provide a pertinent and efficient measurement of elevated levels of evening and nocturnal activity of RLS.11 Moreover, the Motion Logger, with respect to the other actigraphic devices, seems to be more sensitive in detecting small nocturnal movements.14

In a blinded fashion, patients received placebo or cabergoline, starting at 0.5 mg, 2 hours before bedtime and titrated the dose to effectiveness in incremental step of 0.5 mg with a maximum dose of 2 mg. Since the variables did not show a Gaussian distribution, the means of each evaluation (B, T0, T1, T2) for IRLSSG Scale, CGI, and mean nocturnal activity (only for T0, T1 and T2) were compared by means of the non-parametric Friedman test and Dunn’s multiple comparison method.

RESULTS

Ten patients completed the study. Two patients dropped out after the first week of treatment with cabergoline (T1) due to marked nausea (N=1) and ineffectiveness (N=1). For the total group, the mean baseline of the IRLSSG Rating Scale was 23.4 ± 4.4 (range 13-29); RLS was severe in 10 patients (scoring between 21 and 30), and moderate in 2 patients (scoring from 11 to 20). Nocturnal polysomnography confirmed sleep disruption and PLMS in almost all the patients: mean total sleep time was 286.9 minutes (range 92-502); sleep efficiency, 62.5% (21%-97%); sleep latency, 29.9 minutes (2-118 minutes), number of awakenings, 9.3 (2-28), wake after sleep onset (WASO), 134 minutes (7-324); and index of PLMS was 31.4 per hour (2-92). All patients but 1 had a PLMS index above 5 per hour, and 9 of the 12 had periodic limb movements during quiet wakefulness before sleep onset or during WASO. Serum ferritin and iron levels were normal in all of the patients, and none showed any signs of peripheral neuropathy with the electromyography or the nerve conduction study.

All the patients who completed the study reported an improvement in the RLS symptoms with cabergoline versus baseline and placebo (Figure 1). IRLSSG Rating Scale score was similar between baseline and placebo (24.3±4.4 vs 23.1±5.9, P=0.6), but significantly decreased after treatment with cabergoline for 1 week (12.5±6.0) and 2 months (9.8±6.9)(P=0.01 and P=0.001 vs B, and P=0.01 and P=0.005 vs T0, respectively). The CGI of the effect of the drug on RLS (considering the severity of the illness and rating the total improvement in the clinical judgment) moved from no change or minimally improved to much improved or very much improved after cabergoline treatment, for both T1 and T2.

The mean activity value of actigraphy decreased from 19.8±9.3 (T0) to 13.6±6.4 (T1) and to 8.5±5.3 (T2)(P<0.05 between T0 and T2)(Figure 2). The mean dose of cabergoline was 1.1 mg (range 0.5-2.0).

Due to the positive effect of cabergoline on RLS, 9 of the 10 patients chose to continue the drug. One patient had only a small positive effect, and at the end of the 2-month period, he discontinued the treatment. We continued the observation at 6 and 12 months in the 9 patients with an open follow-up study that included flexible doses: the IRLSSG Rating Scale scores were 6.4±5.1 and 6.1±7.6, respectively, showing the persistent efficacy of cabergoline on RLS, with a slight increase of mean dosage (1.3±1.0 mg). Side effects included mild nausea (3 cases), visual hallucination (1 case for only 1 week during the increase of the dosage to 2.0 mg and with disappearance after reduction to 1.5 mg) and peripheral edema (1 case). No augmentation was noted. In 3 patients, despite the improvement of RLS, insomnia persisted, and a drug for sleep induction and maintenance was added during the follow-up period with a good response: 1 patient received clonazepam and 2 patients trazodone.

DISCUSSION

Our data support the results from a dose finding, double-blind, controlled study15 that showed that cabergoline is safe and effective as a single-drug treatment for severe RLS. Compared with placebo, cabergoline showed a positive effect in 11 out of the 12 patients in our study and had a very low incidence of adverse events, with only 1 patient dropping out of the study due to nausea.

By the end of the first week of our study, all the patients treated with cabergoline showed a decrease in RLS severity, as measured by the IRLSSG Rating Scale; the effectiveness of treatment in 9 of the 10 patients who completed the study was even more apparent at 2 months and during long-term follow-up (during the open phase of the trial). The results of the IRLSSG Rating Scale revealed that only 1 patient continue to show severe symptoms with treatment, with a score of 27 at baseline, 31 at T0, 22 (with cabergoline) at T1 and 27 (with cabergoline) at T2. Most patients had a severity score of less than 10 with treatment, providing a persistent positive effect on RLS symptoms. This trend was also evident from the evaluation of actigraphic data; the decrease in mean motor activity in the legs during the night was slight and nonsignificant after 1 week (T1), probably due to the intrinsic properties of the drug, but it was significant in almost all the patients after 2 months of treatment (T2). These data are in accordance with experiments per-

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Figure 1—International Restless Legs Syndrome Study Group Rating Scale score (mean and SD values) at baseline (Basal), at the end of 1 week of placebo (T0 Pla), after 1 week (T1 Cab 1w) and 2 months (T2 Cab 2m) of treatment with cabergoline. *T1 vs Basal P=0.01, T1 vs Pla P=0.01, T2 vs Basal P=0.001, T2 vs Pla P=0.005

Figure 2—Motor activity during the night (as demonstrated by actigraphy worn at the ankle) in arbitrary unit (mean and SD values) during 1 week of placebo (T0 Pla), the first week of treatment with cabergoline (T1 Cab 1w), and the last week of the 2-month period of cabergoline use (T2 Cab 2m). *T0 vs T2 P=0.05.
formed in rats showing a delayed effect in inhibiting basal and reserpine-induced prolactin secretion with the use of cabergoline compared to pergolide and bromocriptine, but with cabergoline showing a more potent aftereffect.16 Whether this effect may be related to the long half-life of the drug or (more probably) is due to a long exposure to the drug is unclear. The rapid peak plasma level of cabergoline (reached within about 1-2 hours after oral administration) and the fact that absorption is relatively unaffected by food intake (amino acids and vitamins) may justify the administration 2 hours before bedtime.17

The efficacy of acute and chronic administration of cabergoline on RLS, shown in approximately 90% of the patients, is quite similar to that reported with other DAs (75%),18,19 but, compared to other DAs, cabergoline does not require a significant increase in dosage over time. We have no direct data regarding the effect of cabergoline on PLMS because we did not monitor our patients with polysomnography after the treatment. However, indirect evidence is provided with our actigraphic data which showed a decrease in leg motor activity during the night after treatment with cabergoline.13 These results are in agreement with the positive effects of other D2- and D3-receptor agonists such as pergolide,14 pramipexole15 and ropinirole20 on leg movements during sleep. Compared with pergolide, cabergoline therapy showed fewer side effects and no augmentation; in addition treatment with cabergoline does not require a long titration period, which is required with the use of pergolide. The dosage of cabergoline during long-term treatment appears to be lower than required for pramipexole and ropinirole (in particular for ropinirole) and, again, shows no evidence of inducing augmentation (8% was reported with the use of pramipexole).8

The lack of patients complaints about sleep during the acute treatment phase of our study (T1 and T2) provides evidence that the use of cabergoline did not affect sleep quality and duration in our study. Although the sleep quality improved along with the amelioration of RLS, 3 patients required additional drug treatment for insomnia during the period of chronic administration of cabergoline even though RLS symptoms were resolved. Insomnia may occur with DA treatment; it has been noted that some D2-receptor agonists may have a role in maintaining wakefulness rather than in inducing sleep.21 Low doses of pramipexole do not significantly affect striatal dopamine release during the first 2 hours following drug administration and, consequently, the increase in sleep and decrease in wakefulness observed with the administration of low DA doses (presynaptic receptor effect) may be retarded or absent.22 We have no objective data to evaluate this subjective finding because polysomnography was not obtained during the drug-treatment period.

Our patients reported side effects similar to those described by patients with Parkinson disease who are treated with cabergoline, but our patients reported side effects that are milder in severity - probably due to the lower doses used in RLS compared to Parkinson disease. During the long-term follow-up period our patients did nor report any tolerance or any consistent side effects that were severe enough to stop the treatment, evidenced by the fact that the mean dose of the drug was not significantly different from that given during the first 2-month period. No patients complained of sleep attacks during the day or excessive daytime sleepiness, a finding that is in accordance with the results of other DA used for the treatments for RLS.22,23 Recently, however, single cases of daytime fatigue and sedation have been reported in patients with RLS who are treated with pergolide.24

A further relevant finding of our study is the lack of augmentation during the chronic treatment. Augmentation has been described only with the use of DAs in the treatment of RLS (specifically with L-dopa, pergolide and pramipexole) and is consistent with an anticipation of the RLS symptoms, early during the evening or during the day, with a possible increase in severity. The pathogenic mechanism responsible for this phenomenon is not yet completely understood. It has been shown that the incidence of augmentation is greater in patients with severe RLS and in those taking higher doses of the drugs (ie, L-dopa) but has also been reported with the use of pergolide and pramipexole at lower dosages, although to a lesser degree and severity.7,8 A possible explanation for the lack of augmentation in our RLS patients may be the long half-life of cabergoline; the other DAs with short or intermediate half-life may produce a strong receptor stimulation that rapidly alternates with neurotransmitter vacancy, thus inducing a phenomenon similar to that responsible for motor dyskinesia or complication in patients with Parkinson disease. Other possible factors involved in augmentation such as concomitant iron deficiency, other pathologies that are not related to RLS, and the prevalence of secondary versus primary forms of RLS could not be investigated because all of our patients had idiopathic RLS. A possible alternative explanation may be that the number of patients in this study is too small and the length of the study is too short to see an augmentation effect. However, augmentation has been reported to occur from 1 to 4 months after the instituting treatment with other DAs.7,8

Our study was not a randomized, double-blind, placebo-controlled, crossover trial. Thus, some effects of cabergoline on RLS symptoms may be due to the method of administration (the first week of placebo followed by the drug) or to the different size of the pills (the cabergoline tablet was smaller in size than the placebo). However, we did not note a significant placebo effect on the patients’ responses to the IRLSSG Rating Scale, probably because our patients had a moderate to severe form of RLS. We also have no data on the effect of cabergoline on sleep structure and on PLMS index, only the support from the actigraphy. Although studies using actigraphy to evaluate PLMS in RLS are rare and no actigraphic instrument has been validated for RLS-PLMS, it seems helpful and promising to quantify leg motor activity both in wakefulness (as with periodic limb movements during wakefulness and non-periodic activity) and during sleep (PLMS).13 Preliminary reports on validation versus polysomnography have shown reliability of the instrument for following a change in symptoms of RLS patient but the device is not sufficiently sensitive and specific enough to be used for diagnosis.31

In conclusion, our study confirms the efficacy of cabergoline, a dopaminergic agent with a long half-life, as single drug for patients with moderate to severe RLS and for short-term to intermediate-term treatment. Moreover, as opposed to L-dopa and other DAs, cabergoline seems to be relatively safe and causes less augmentation, suggesting a relevant role in RLS treatment. Conducting a double-blind, randomized, long-term, crossover study using polysomnography with a larger sample of patients is necessary to confirm our preliminary data on RLS and clarify the effect on sleep and PLMS.

REFERENCES

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