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Sleep Medicine 3 (2002) S23–S25

SLEEP MEDICINE

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Restless legs syndrome augmentation and pramipexole treatment

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Abstract

Objective: To evaluate in an open-label clinical series the occurrence of restless legs syndrome (RLS) augmentation in 60 consecutive RLS patients treated with pramipexole (PPX) for at least 6 months.

Background: In patients with restless legs syndrome (RLS), augmentation is most commonly seen with long-term use of levodopa and pergolide.

Method: Open-label clinical series in 60 consecutive RLS patients treated with PPX for at least 6 months.

Results: Augmentation was observed in five patients (8.3%) after 4–15 weeks of treatment. Augmentation occurred more frequently in patients with secondary RLS (4/21) than in those with idiopathic RLS (1/39).

Conclusions: Augmentation is unrelated to either severity of RLS or doses of PPX. There is a very low optimal therapeutic dose of PPX (0.25 mg/day) in most RLS patients (66%).

Keywords: Restless legs syndrome; Pramipexole; Augmentation

1. Introduction

Several recent studies have shown that dopaminergic medications provide dramatic symptomatic improvement for restless legs syndrome (RLS). However, relatively little is known about the long-term consequences of this treatment. The putatively intact nigrostriatal dopamine system in RLS patients might explain the lack of complications that usually affect patients with Parkinson's disease (PD) treated with the same dopaminergic compounds (e.g. dyskinesias) [1,2].

The two significant complications of long-term treatment with dopaminergic agents reported in RLS patients are the rebound of symptoms and augmentation [3]. Rebound is the tendency of symptoms to worsen at the end of a dosing period, leading to late-night or morning recurrence of symptoms. This complication is most commonly seen when the regular-release formula of levodopa/carbidopa is used. The second complication, referred to as RLS augmentation, is the apparent worsening of symptoms after long-term use of dopaminergic medications. Augmentation consists of progressively earlier daily onset of symptoms (in the afternoon or evening) and of expansion of symptoms beyond the legs (e.g. upper limbs). Augmentation may be seen as an increase in symptom intensity or a decrease in drug efficacy. Increasing medication dosage may lead to greater augmentation, while discontinuing medication will return the patient's symptoms to baseline level. Allen and Earley [4] were the first to describe augmentation and reported its occurrence in 82% of RLS patients treated with levodopa/carbidopa. The augmentation was greater in patients with more severe RLS and with a higher dose of medication. The same complication has been reported in 15–25% of patients treated with pergolide, a D_1/D_2 receptor agonist [5,6].

Recently, the newly-developed D_3 receptor agonist pramipexole (PPX) was found to be effective in the treatment of patients with PD [7]. PPX is not an ergoline derivative and it is an antiparkinsonian compound better tolerated by PD patients than the medications derived from ergoline. A recent paper reported that PPX did not cause augmentation in seven RLS patients followed for a mean of 7.8 months [8]. The aim of this open-label clinical study was to evaluate the occurrence of augmentation in RLS patients treated with PPX for at least 6 months.

2. Methods

We included consecutive RLS patients recruited from the Sleep Disorders Center of Scientific Institute H. San Raffaele, in Milan. The exclusion criteria included patients who were pregnant or who experienced persistent beneficial effects of drugs for RLS.

RLS diagnosis was made according to the International Classification of Sleep Disorders [9], and the RLS severity

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1389-9457/02/$ - see front matter
PII: S1389-9457(02)00144-2

scale developed by the International Restless Legs Syndrome Study Group [10] was administered to each patient. RLS patients were classified as having either secondary or idiopathic RLS based on medical history, clinical examination, and appropriate blood testing. In the presence of any condition known to be associated with RLS – specifically anemia, low ferritin levels, chronic renal failure, peripheral neuropathy, or myelopathy – patients were classified as having secondary RLS. Written informed consent was obtained from each patient, and the ethics committee approved the study.

Each patient initially received PPX at a dosage of 0.125 mg, administered 60–90 min prior to bedtime. Patients were instructed to increase the dosage by 0.125 mg each week until satisfactory relief of RLS symptoms was obtained or adverse events prevented further increase.

3. Results

Sixty patients were included in the study, 39 with idiopathic RLS and 21 with secondary RLS. The mean age was 58 years (range 37–90); mean RLS duration was 28 years (range 0.5–50); and mean RLS severity scale score was 19 (range 8–33). All included patients had only nighttime symptoms.

Fifty-one patients had been previously treated with other medications: clonazepam ($n = 29$), gabapentin ($n = 17$), levodopa ($n = 15$), pergolide ($n = 15$), and various other compounds ($n = 19$). Patients using other medications at the time of study initiation (12 were taking clonazepam and three were taking levodopa) were not allowed to change their doses. At the time of evaluation for RLS augmentation, the PPX dose was variable: 0.25 mg in 40 patients, 0.5 mg in seven patients, and 1.0 mg in 13 patients.

RLS augmentation was observed in five patients (one with idiopathic RLS and four with secondary RLS) with a mean age of 58 years (range 49–75), a mean RLS duration of 24 years (range 11–30), and a mean RLS severity scale score of 21 (range 9–29). The PPX doses and the appearance time of augmentation are reported in Table 1. No difference was found between patients with and without augmentation, except for the higher frequency of secondary forms of RLS compared to idiopathic forms of RLS in the 'augmentation' group ($P = 0.04$, Fisher test). No correlation was found between serum ferritin levels and augmentation: all patients with augmentation had ferritin levels within the normal range.

Table 1
Occurrence of RLS augmentation

No. of subjects	Treatment duration (weeks)	Type of treatment (mg/day)
1	4	Pramipexole 0.25 and levodopa/carbidopa 100/25
2	8	Pramipexole 0.25
1	12	Pramipexole 0.25
1	15	Pramipexole 0.25 and levodopa/carbidopa CR 100/25

The patients reported very few side effects. Those that were reported included mild nausea during the first 2–3 weeks of treatment in three patients; excessive daytime sleepiness (without the 'sleep attacks' that have been described in PD patients treated with dopaminergic compounds [11]) in two patients irregularly throughout the 6-month period (one patient with 0.5 mg/day PPX, the other patient with 1.0 mg/day PPX); and mild sedation in four subjects (one patient with 0.25 mg/day PPX; two with 0.5 mg/day PPX; and one with 1.0 mg/day PPX plus an evening dose of 0.5 mg clonazepam).

4. Conclusions

Augmentation is the most serious common complication associated with levodopa therapy of RLS. The exact mechanisms causing augmentation are not known. A common and successful treatment approach has been to change levodopa to another dopaminergic agent. Generally, the augmentation does not reoccur upon switching to a dopamine agonist [5].

This study shows that RLS augmentation (1) occurs in a very low percentage of patients treated with PPX (8.3%), (2) seems to be unrelated to the dose of medication, (3) occurs within the first 4 months of treatment, and (4) is not influenced by the severity of RLS before the onset of PPX treatment. However, in this study, augmentation seems to be more frequent in secondary RLS compared to idiopathic RLS. Thus, the two factors that seem to most strongly affect the risk of augmentation are (1) treatment with levodopa rather than a dopamine agonist, and (2) RLS occurring as secondary to other conditions rather than idiopathic RLS.

Other dopaminergic agonists, such as pergolide [5,12] and ropinirole [13], have been found to be effective in the treatment of RLS. However, in our study we observed a very low optimal therapeutic dose of PPX (0.25 mg/day) in a large percentage of our patients (66%). Moreover, we observed a very rapid efficacy of the drug on RLS symptoms. In fact, about 50% of patients reported moderate or marked improvement just after the first to third administration of PPX. The rapid efficacy of PPX at a very low dosage seems to indicate that D_3 receptors of the mesolimbic system may be more specifically involved in the pathophysiology of RLS, as has been suggested by other authors [8].

Future long-term studies with ropinirole (a dopamine agonist with relatively greater D_3 and D_4 affinity than pergolide or bromocriptine) and with cabergoline (a D_2 agonist with half-life > 65 h) may clarify whether or not the elimination half-life and/or specific receptor activity of different dopaminergic agents are crucial for developing the augmentation phenomenon in RLS.

References

[1] Von Scheele C, Kempi V. Long-term effect of dopaminergic drugs in restless legs: a 2 year follow-up. Arch Neurol 1990;47:1223–1224.

[2] Becker PM, Jamieson AO, Brown WD. Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: response and complications of extended treatment in 49 cases. Sleep 1993;16:713–716.

[3] Hening W, Allen R, Earley C, Kushida C, et al. The treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999;22:970–999.

[4] Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996;19:205–213.

[5] Earley CJ, Allen RP. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. Sleep 1996;19:801–810.

[6] Silber MH, Shepard Jr JW, Wisbey JA. Pergolide in the management of restless legs syndrome: an extended study. Sleep 1997;20:878–882.

[7] Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson's disease: a randomized dose-ranging study. J Am Med Assoc 1997;278:125–130.

[8] Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol 2000;Suppl 1:27–31.

[9] American Sleep Disorders Association, Diagnostic Classification Steering Committee. The international classification of sleep disorders, revised: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association, 1997.

[10] Hening WA, Walters AS, Rosen R, LeBroca C, et al. The International RLS Study Group Rating Scale: a reliable and valid instrument for assessing severity of RLS [abstract]. Neurology 2001;56(Suppl 3):A4.

[11] Frucht S, Roger JD, Greene PE, Gordon MF, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908–1910.

[12] Winkelmann J, Wetter TC, Stiasny K, Oertel WH, et al. Treatment of restless legs syndrome with pergolide: an open clinical trial. Mov Disord 1998;13:566–569.

[13] Ondo W. Ropinirole for restless legs syndrome. Mov Disord 1999;14:138–140.