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Original Article

A dose-ranging study of pramipexole for the symptomatic treatment of restless legs syndrome: Polysomnographic evaluation of periodic leg movements and sleep disturbance

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ABSTRACT

Objective: To evaluate, both polysomnographically and by subjective scales, the efficacy and safety profile of pramipexole for restless legs syndrome (RLS) via a 3-week, double-blind, placebo-controlled, parallel-group, dose-ranging study.
Methods: At baseline and after 3 weeks, periodic limb movements (PLM) and sleep parameters were assessed by polysomnography, and patients self-assessed their sleep disturbance and overall RLS severity using the international RLS study group rating scale (IRLS). Four pramipexole doses were evaluated: 0.125, 0.25, 0.50, and 0.75 mg/d. Data from 107 patients were included in the intent-to-treat (ITT) analysis.
Results: For pramipexole recipients, the primary outcome measure, PLM per hour in bed asleep or awake (the PLM index, or PLMI), decreased by a median of −26.55 to −52.70 depending on dosage group, vs. −3.00 for placebo ($p < 0.01$ or $\leqslant 0.001$ for each group vs. placebo; Wilcoxon–Mann–Whitney test). Improvements in the secondary endpoints of PLM while asleep and while awake were also significantly superior for pramipexole. At 3 weeks, all pramipexole doses reduced the median for PLM while asleep to levels considered normal (<5 PLM/h). Except for delta-sleep time and awakenings/arousals, sleep parameters remained unchanged or favored pramipexole. Median sleep latency was reduced by −5.00 to −11.75 min in the pramipexole groups, vs. −2.00 for placebo ($p < 0.05$ for all groups except 0.25 mg/d). Median total sleep time increased by 25.75–66.75 min, vs. 25.50 ($p < 0.05$ for 0.50 mg/d), and median time in stages 2–4/rapid eye movement (REM) sleep increased by 37.00–68.00 min, vs. 26.75 ($p < 0.05$ for 0.50 mg/d). By subjective IRLS ratings, all pramipexole doses were significantly superior to placebo. Safety analysis demonstrated no dose-dependent increase in adverse events, and no drug-related increase in daytime somnolence was observed.
Conclusions: Pramipexole is effective and well tolerated in RLS, most notably among objective measures, for reducing PLM and decreasing sleep latency. Although other sleep parameters showed lesser, usually insignificant change, patients' subjective ratings of RLS severity and sleep disturbance were significantly improved ($p \leqslant 0.0023$).

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an urge to move the legs, generally in association with or in an attempt to relieve paresthesia or dysesthesia in the lower extremities [1]. Worsening of symptoms occurs during periods of inactivity, especially at night, resulting in sleep disruption that

Abbreviations: BP, indicates blood pressure; ESS, Epworth sleepiness scale; IRLS, international RLS study group rating scale; ITT, intent-to-treat; PLM, periodic limb movements; PLMAI, periodic limb movements during sleep with arousal index; PLMI, periodic limb movements during time in bed index; PLMSI, periodic limb movements during sleep index; PLMWI, periodic limb movements during wakefulness index; REM, rapid eye movement; RLS, restless legs syndrome; TST, total sleep time.

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can negatively impact cognitive function [2] and reduce quality of life to an extent comparable to that associated with other chronic diseases, such as diabetes, depression, and osteoarthritis [3].

The overall prevalence of RLS is approximately 5–10%. Occurrence of the disorder increases in older age groups and among women (approximately 2:1 ratio, women:men) [4,5]. Importantly, there is a significant under diagnosis of RLS. Despite physician consultations by individuals with RLS symptoms, few patients actually receive a diagnosis of RLS [4]. In a study comparing RLS sufferers with matched controls, only 6.2% (21/146) of those termed RLS sufferers received a diagnosis of RLS [5].

Neither the etiology nor the pathophysiology of RLS has been fully elucidated. However, the involvement of dopaminergic pathways has been suggested by neuroimaging [6], as well as by the demonstrated efficacy of dopamine agonists and their recommendation as first-line pharmacologic therapy for symptomatic relief of RLS [7–10].

Although levodopa has been the most studied dopaminergic agent for the treatment of RLS, its long-term use is limited by risk of augmentation – that is, a worsening of RLS symptoms. Augmentation and rebound (i.e., an early morning recurrence of RLS) may develop in up to 70% and 35% of patients respectively taking levodopa [8], complicating the long-term use of this agent for the treatment of RLS. Our group and others have demonstrated the efficacy of pramipexole, a second-generation, nonergot dopaminergic agent, for the treatment of RLS [11–14]. The purpose of this polysomnographic investigation was to confirm the symptomatic efficacy of pramipexole with regard to changes in nocturnal periodic limb movements (PLM) and to further evaluate the efficacy of pramipexole for RLS-associated sleep disturbance.

2. Methods

2.1. Patient population

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District. Written informed consent was obtained for all patients prior to participation.

Adult patients ($\geqslant$18 years of age) with idiopathic RLS were eligible for the study. Inclusion criteria included the presence of all 4 international RLS study group criteria for the diagnosis of RLS [15]; moderate or severe symptoms, defined as a score of $\geqslant$15 on the international RLS study group rating scale (IRLS) [16]; a PLM frequency $\geqslant$5 times/h during time in bed, documented by polysomnography; and weekly sleep disturbances due to RLS within the prior 3 months. Exclusion criteria included any of the following: the presence of contraindications to the use of pramipexole; the presence or evidence of other sleep disorders, substance abuse, or comorbid conditions that may cause or exacerbate RLS or interfere with its assessment; the use of medications that may influence the course of RLS; participation in an investigational drug study within the previous 2 months; and current use (within the previous week) of any RLS therapy. Pregnancy or breast-feeding were also causes for exclusion, and females of childbearing potential and males were required to use adequate contraception.

2.2. Study design and endpoints

This single-center dose-ranging study used a double-blind, placebo-controlled, parallel-group design to evaluate the efficacy and safety of pramipexole for the treatment of patients with RLS. The study duration was 3 weeks, and 4 pramipexole doses were evaluated: 0.125 mg, 0.25 mg, 0.50 mg, and 0.75 mg, in which 0.125 mg salt was equivalent to 0.088 mg base.

After completing an initial assessment that included polysomnographic evaluation to establish baseline values for all polysomnography-assessed endpoints, patients were randomly assigned to placebo or to one of the pramipexole doses in a 1:1:1:1:1 ratio. Pramipexole therapy was initiated at 0.125 mg and was titrated to the assigned dose in 4-day intervals. The once-daily doses were administered orally 2–3 h before bedtime.

The primary efficacy endpoint, assessed after 21 days of treatment, was the change from baseline in periodic limb movements during time in bed index (asleep or awake; PLMI). Secondary efficacy endpoints, also evaluated at baseline and after 3 weeks of treatment, included subjective assessment using the IRLS [16], and objective assessments of PLM and sleep architecture using polysomnography. Assessments of PLM included the PLM during sleep index (PLMSI), the PLM during wakefulness index (PLMWI), the PLM during sleep with arousal index (PLMAI), the total number of PLM, the total number of PLM during sleep, the total number of PLM during sleep with arousal, and the total number of awakenings/arousals during sleep. Endpoints utilized for the evaluation of sleep and sleep architecture included sleep latency, sleep efficiency, total sleep time (TST), time and percentage of time spent in delta sleep, and percentage of sleep spent in rapid eye movement (REM) sleep.

All polysomnographic evaluations were performed in single sound- and light-isolated bedrooms according to the American Sleep Disorder Association guidelines for the diagnosis and evaluation of RLS [17,18]. This included the use of appropriate channels to monitor electroencephalography, electro-oculography, chin electromyography, and the left and right anterior tibialis surface for leg movements. Recordings were begun at the time of "lights off." After 8 h, the patients were awakened, if asleep, and the recordings were stopped ("lights on").

Safety was assessed by the reported incidence and severity of adverse events, as elicited from patients by nonprobing questions, as well as from clinical test results (i.e., vital signs, electrocardiogram, blood count and/or chemistry, and urinalysis). The recording of adverse events was conducted without regard to causality. A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required (or prolonged) a patient's hospitalization, was a congenital anomaly/birth defect, or was deemed serious for any other reason representing a significant hazard.

Somnolence during daily activities was considered to be a significant adverse event. Additionally, the Epworth sleepiness scale (ESS) was used at baseline and after 3 weeks to evaluate the potential effect of pramipexole on daytime sleepiness [19]. This self-report instrument measures the likelihood of dozing off or falling asleep in 8 different situations on a 4-point rating scale (from "no chance" to "high chance"). The items are summed to yield a total score (range, 0–24); higher scores are indicative of greater daytime somnolence, and scores $\leqslant$ 10 are considered within the normal range [19].

2.3. Data Analyses

Since the intent-to-treat (ITT) principle was utilized, every effort was made to collect complete polysomnographic and other efficacy data both at baseline and after 3 weeks. For missing efficacy data, a last-observation-carried-forward approach was used, except for patients discontinuing treatment due to unexpected worsening of RLS, in which case missing data were imputed using the least favorable data prior to discontinuation. Continuous or discrete variables were analyzed by descriptive statistics or frequency tables, respectively.