Night-time use of rotigotine in advanced Parkinson’s disease

Margherita Canesi, MD
Claudio B. Mariani, MD
Ioannis U. Isaiaes, MD
Gianni Pezzoli, MD

* Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy
** Department of Physiology, University of Milan, Italy

Corresponding author: Margherita Canesi
Centro Parkinson, Istituti Clinici di Perfezionamento
Via Bignami 1, 20126 Milan, Italy
E-mail: canesi@parkinson.it

Summary

Transdermal rotigotine was used in six patients with advanced Parkinson’s disease and sleep disorders (UPDRS part II item 12 score ≥2) receiving oral levodopa and diurnal apomorphine infusions. Transdermal rotigotine (2-4 mg/24h) was used at night for four months.

Sleep disorders improved, the total Parkinson’s Disease Sleep Scale score falling by an average of 45%; significant improvements emerged in the items quality of sleep and difficulty in remaining asleep (p<0.05). No undesirable dopaminergic effects were reported.

This preliminary open-label study suggests that transdermal rotigotine may be a well tolerated and effective treatment in patients with advanced Parkinson’s disease, reducing nocturnal disability and ameliorating sleep disorders without inducing undesirable dopaminergic effects.

KEY WORDS: Parkinson’s disease, rotigotine, sleep disorders

Introduction

Sleep disorders are amongst the most common non-motor symptoms in Parkinson’s disease (PD). They occur throughout all the stages of the disease, including the pre-motor stage, and their frequency ranges from 47.9% in Hoehn and Yahr stage 1 to 81.6% in Hoehn and Yahr stage 4-5 (1). The etiology of sleep disorders in PD is still controversial, as multiple factors contribute to their occurrence whose relative importance has not been established. These factors include PD-related motor symptoms, psychiatric symptoms related to the disease itself or to antiparkinson treatment, and other sleep disorders, such as alterations of normal sleep architecture due to aging, REM sleep behavior disorder and restless legs syndrome (2). PD-related motor symptoms include nocturnal akinesia, early-morning akinesia, difficulty turning in bed, dystonia, painful cramps and tremor. These nocturnal symptoms are the manifestation of motor fluctuations and are often related to low-dose dopaminergic treatment (2).

Sleep disorders in PD require treatment, as they reduce quality of life by causing daytime tiredness, fatigue and irritability and put patients at risk of excessive daytime sleepiness (2). The main therapeutic strategy for resolving sleep disorders due to PD-related motor symptoms is to preserve nocturnal mobility through maintenance of adequate blood concentrations of dopaminergic agents throughout the night and through to morning. Immediate or controlled release formulations of levodopa together with catechol-O-methyltransferase (COMT) inhibitors administered in the evening or during the night may ameliorate motor symptoms, but their duration of efficacy does not exceed three hours (3).

Long-acting dopamine agonists, such as cabergoline, allow more stable dopaminergic stimulation and improve nocturnal mobility (4,5). However, the use of ergot-derived dopamine agonists, including cabergoline, has proved to be associated with valvular heart disease (6) and is no longer recommended. Subcutaneous apomorphine also allows an increase in the hours of sleep, even at low doses (7). However, it requires the use of a pump, which is impractical at night; moreover, this approach entails a greater apomorphine dosage, which is often associated with an increase in untoward dopaminergic and skin reactions.

Rotigotine is a highly soluble and highly lipophilic non ergot-derived dopamine agonist, which is formulated in transdermal systems delivering 2, 4, 6 or 8 mg over 24 hours; it is approved for therapeutic use either alone in the early stages of PD or in combination with levodopa and other antiparkinson agents in the more advanced stages of the disease, at dosages ranging from 2 to 16 mg/24h. Pharmacokinetic studies have shown that it is able to cross the stratum corneum and epidermis and reach clinically effective concentrations in the bloodstream. The transdermal system guarantees constant release of the drug, resulting in stable blood concentrations. It therefore avoids the characteristic peaks and troughs that occur after oral drug administration and produce so-called “pulsatile” stimulation of dopamine receptors, which is believed to be one of the main pharmacodynamic mechanisms underlying long-term levodopa complications (8,9).

We assessed the efficacy of transdermal rotigotine in resolving nocturnal motor disability in six patients with advanced PD treated with subcutaneous apomorphine during the day.

Methods

Eligible patients had PD diagnosed according to UK Brain Bank criteria (10), reported sleep disorders asso-
associated with a Unified Parkinson’s Disease Rating Scale (UPDRS) part II item 12 score ≥2, and were on oral treatment with levodopa plus diurnal treatment with apomorphine by subcutaneous infusion (12 hours a day) on account of motor fluctuations. Patients with dementia (Mini Mental State Examination, MMSE <24), psychosis or hallucinations were excluded, as were patients whose levodopa or apomorphine dosage regimen had been changed in the two months prior to recruitment. All the patients gave their informed consent to take part in the study.

The subcutaneous apomorphine was given from 8.00 a.m. to 8.00 p.m.; transdermal rotigotine was applied at 7.00 p.m. and removed at 7.00 a.m., before starting the subcutaneous infusion of apomorphine. The patch applied during the first week of treatment released 2 mg/24h. The patient was instructed to call the neurologist if sleep disorders persisted at the end of the first week; the neurologist could decide to increase the dosage by 2 mg/24h up to 4 mg/24h. A further increase, to 6 mg/24h (the maximum dose), was allowed at the end of the third week following the same procedure. Thereafter, treatment had to be continued at the same dosage until the end of the study. Efficacy was measured using the Parkinson’s Disease Sleep Scale (PDSS) (11) and a visual analogue scale (VAS: 0=impossible to sleep, 10=slept soundly all night) to quantify sleep problems at baseline and after four months of treatment.

The UPDRS motor score was also measured in the ON state to verify any impact on motor function. Safety was monitored by adverse event reporting. Data are reported as means and standard deviations. The statistical analysis was performed using the JMP program. Scores after four months of treatment were compared with baseline scores using Tukey’s test, setting p<0.05 as the cutoff for statistical significance.

**Results**

Five men and 1 woman were included in the study. Their mean age was 60.4±7.8 years (range: 52-75 years), the mean duration of PD was 17.4±3.2 years (range 14-22 years) and their mean age at onset was 43.0±7.7 years (36-55 years). All the patients were taking oral levodopa (mean dosage: 600±70.7 mg daily) and were receiving apomorphine by infusion during the day (mean dosage: 3.1±0.8 mg/h for 12 hours).

One patient discontinued rotigotine because of inefficacy after one month of treatment.

The other patients continued treatment with rotigotine for four months. Three continued applying the lowest strength (2 mg/24h) throughout the study, while the other two increased the dosage once, to the 4 mg/24h patch. The PDSS data (single item scores) are shown in figure 1. The total PDSS score fell from 21.2±2.8 to 11.7±2.8 (on average -44.8%, p<0.05). Improvements were recorded in 12 of the 15 items of the scale. The improvements in the items quality of sleep and difficulty in staying asleep were significant: the mean quality of sleep score improved by 1.4 at the end of treatment; the mean score related to difficulty in staying asleep fell from 3.0±1.2 to 1.0±0.7 at the end of treatment (both p<0.05). The mean VAS score improved from 2.6±3.6 to 7.4±0.6 (+65%).

The mean UPDRS motor score improved slightly from 25.4±7 at baseline to 26.2±6 at the end of treatment. No serious adverse events were reported and no patient discontinued treatment because of intolerance.

![Figure 1 - Single PDSS item scores](image-url)
one patient reported mild irritation at the site of application of the rotigotine patch (4 mg/24h); this event did not cause discontinuation of the treatment.

Discussion

Transdermal rotigotine at low dosages (2-4 mg/24h) was well tolerated and effective in improving sleep in five out of six patients with advanced PD who needed a combination of oral levodopa and subcutaneous diurnal apomorphine infusion to control motor symptoms. Indeed, the PDSS results showed that overall sleep improved, on average, considerably (total score: -45%) and that two key items – quality of sleep and difficulty in staying asleep – improved significantly without a worsening of item 7 (distressing hallucinations), which is a typical adverse effect of excessive dopaminergic treatment (2). Thus, rotigotine, in a low-strength patch (2-4 mg/24h), appears to be the correct drug to add to the combination of oral levodopa plus subcutaneous apomorphine infusion in patients with advanced PD, guaranteeing stable dopaminergic concentrations throughout the night (9,12,13).

Two open-label studies on the use of transdermal rotigotine for sleep disorders in PD are mentioned in the literature. Their results appear to be consistent with ours. In the study by Antonini et al. (13) the disease was, on average, less advanced than in our patients (mean disease duration: 10.4±5 years, range: 8-14 years), even though those authors’ patients were on average older than our patients (mean age 68.2±8 years), and were on dopaminergic treatment with oral levodopa and oral dopamine agonists (pramipexole n=6 and ropinirole n=4). Transdermal rotigotine was applied in the evening and removed in the morning, as in our study, but higher dosages were used (4-8 mg/24h). The follow up was shorter than in our study (1 vs 4 months). The total PDSS score improved to a lesser degree than in our study (-18% vs -45%) and no adverse effects were reported. No information on single PDSS scores are provided. The difference in efficacy may have been due to the shorter duration of the treatment in the patients of Antonini et al. and also to the fact that their patients were, on average, in a less advanced stage of PD than our patients. In the other study by Giladi et al., which is mentioned in the review of rotigotine by Chen et al. (9), rotigotine, at unspecified dosages, significantly improved PDSS scores, episodes of nocturia per night, nocturnal akinesia, dystonia and cramp scale scores and ESS scores in 46 PD patients (no data given). No information is provided on the characteristics of the patient population. In addition, rotigotine was recently shown to be effective in improving nocturnal sleep and early-morning motor function in a multinational, double-blind, placebo-controlled trial involving 287 PD patients (the RECOVER study) (12). In this study the PDSS score showed an average improvement of -31.5% vs baseline (p<0.0001 vs placebo), as compared to the -44.8% recorded in our study, even though those patients were given higher doses of rotigotine (2-16 mg/24h vs 2-4 mg/24h). Significant improvements in 10 items of the PDSS scale were reported vs 12 items in our study. Once again, the more pronounced improvement in our study may be due to the fact that we included patients with much more advanced disease (on average 17.4 years vs 4.6 years in the RECOVER study). We decided to conduct our study in a subgroup of patients with very advanced PD, because these subjects often report sleep disorders and are rarely included in clinical trials. One limitation of our study is the small sample size and the fairly short follow up (4 months). We cannot exclude the possibility that the effects observed could change in the long term. This is an important consideration, as the duration of treatment in most studies with rotigotine did not exceed six months and the drug has not been on the market for many years.

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References


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