

EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

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CONTINUOUS DELIVERY OF ROPINIROLE: IMPROVING THE MANAGEMENT OF PARKINSON'S DISEASE

Considerable areas of unmet need remain in the treatment of Parkinson's disease (PD). Although levodopa is the gold standard of treatment for motor symptoms, it is frequently associated with motor complications: 30% of patients will experience these within three years of starting levodopa therapy. This rises to 70% in young-onset patients. There is also a need for a holistic approach to PD that encompasses nonmotor symptoms, which can have a significant impact on patients' quality of life both during the day and at night.

Continuous dopaminergic stimulation: easing the burden of Parkinson's disease

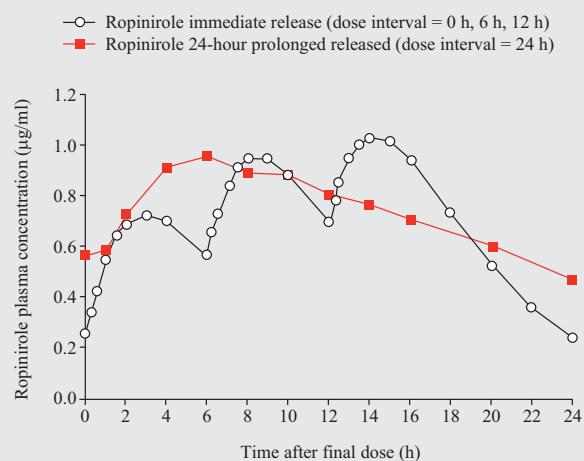
The concept of continuous dopaminergic therapy has arisen from advances in our understanding of the pathophysiology of PD. In healthy brains, striatal dopamine concentrations are fairly constant and dopamine receptors are thought to be more or less continuously activated. Because of their short plasma half-life, conventional delivery of short-acting dopaminergic agents results in peaks and troughs of dopamine concentration, leading to pulsatile stimulation of the dopamine receptors. This alters neuronal firing in the basal ganglia and is thought to be the cause of motor complications such as dyskinesia and 'on/off' fluctuation, said Heinz Reichmann (Department of Neurology, Dresden University of Technology, Dresden, Germany). In particular, using multiple doses of short-acting agents results in a decline in drug concentration at night, and a consequent wearing off of symptom control that can seriously affect patients' quality of life. More continuous delivery of dopaminergic agents should reduce the fluctuation in plasma drug concentration and avoid pulsatile stimulation. This in turn could be expected to reduce or delay the risk of motor complications. Another advantage of long-acting agents is that patients need to take fewer doses. This reduces the complexity of the medication regimen and is likely to improve adherence.

Duodenal infusion of levodopa and use of an apomorphine pump have both been shown to reduce fluctuations in plasma concentration, reduce 'off' time and reduce the incidence of dyskinesia. However, these approaches are invasive and are not practical for most patients.

Continuous delivery of ropinirole: clinical perspectives

A new formulation of the dopamine agonist ropinirole has been developed that provides continuous delivery of ropinirole over 24 hours with a once-daily oral dose. It is known as ropinirole 24-hour prolonged release. Fabrizio Stocchi (Department of Neurology, Scientific Institute for Research, Hospitalization and Health Care IRCCS San Raffaele, Rome, Italy) reviewed the pharmacokinetics, efficacy and safety of this new formulation.

Figure 1 PLASMA CONCENTRATION–TIME PROFILE: ROPINIROLE 24-HOUR PROLONGED RELEASE VERSUS ROPINIROLE IMMEDIATE RELEASE

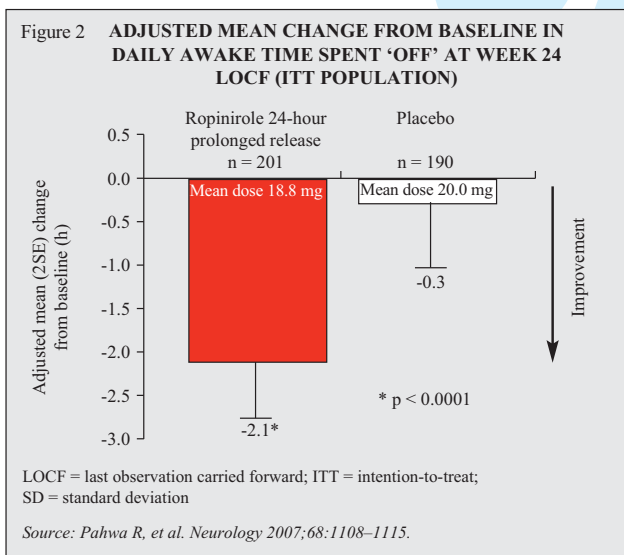


Source: Stocchi F. Data presented at the XVIIth WFN World Congress on Parkinson's disease. Amsterdam, The Netherlands, 2007.

The pharmacokinetics of ropinirole 24-hour prolonged release were studied in a phase II, open-label, randomised crossover study in patients with early PD. Patients received either 8 mg of ropinirole once daily or 2.5 mg of ropinirole immediate release three times daily (every eight hours or at hours 0, 6 and 12). Ropinirole prolonged release gave continuous delivery over a 24-hour period, forming a smooth plasma concentration curve (Figure 1)^[1]. Its pharmacokinetics were only minimally affected by food intake. Total ropinirole exposure was similar for the two formulations. Patients were able to switch overnight from ropinirole immediate release to an equivalent daily dose of ropinirole prolonged release while maintaining similar average daily exposure.

The efficacy and safety of ropinirole 24-hour prolonged release in early PD patients was studied in the Efficacy and Safety in Parkinson's Disease (EASE-PD) monotherapy study. This was a multicentre, randomised, double-blind study in 289 patients, designed to demonstrate the noninferiority of ropinirole prolonged release to ropinirole immediate release. Patients took both treatments, in a three-period crossover design. Switching between treatments was done overnight. The primary end point was mean change from period baseline in UPDRS total motor score. The study showed that ropinirole 24-hour prolonged release is effective as monotherapy, and is noninferior to ropinirole immediate release. Both were generally well tolerated, and there were no statistically significant differences in adverse events between the treatments. Patients successfully switched overnight from ropinirole immediate release to the nearest equivalent total daily dose of ropinirole prolonged release, without loss of efficacy or tolerability^[1].

The EASE-PD Adjunct study was carried out in patients with advanced PD who were not optimally controlled with levodopa^[2]. The primary end point was mean change from baseline at week 24 (last observation carried forward) in daily awake time spent 'off'. Patients were randomised to receive either ropinirole 24-hour prolonged release (n = 201) or placebo (n = 190) in addition to levodopa for six months.

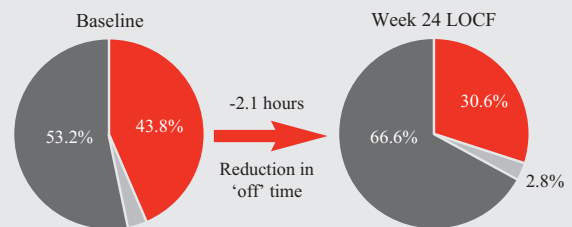


The mean reduction in 'off' time with ropinirole 24-hour prolonged release was 2.1 hours, compared with 0.3 hours with placebo (p < 0.0001; Figure 2). 'Off' time at baseline was 7.0 hours in each group. The ropinirole group also had a significantly greater amount of daily 'on' time spent without troublesome dyskinesias (Figure 3). Mean daily dose of levodopa was decreased from baseline in both groups, with a significantly greater decrease in the ropinirole group. In the trial's secondary end points, there were statistically significant benefits with ropinirole compared with placebo in terms of Unified Parkinson's Disease Rating Scale (UPDRS) total motor score, UPDRS activity of daily living (ADL) score, Beck Depression Inventory (BDI-II) total score, and Parkinson's disease sleep scale (PDSS) total score. There was no significant difference in Epworth Sleepiness Scale (ESS) total score. There was no difference in the incidence of serious adverse events between the two groups, although there was a trend towards more dopaminergic side effects such as dyskinesia and nausea with ropinirole^[2].

Figure 3 CHANGES IN QUANTITY AND QUALITY OF 'ON' TIME WITH ROPINIROLE 24-HOUR PROLONGED RELEASE WHEN ADDED TO LEVODOPA THERAPY IN THE EASE-PD ADJUNCT STUDY

- Ropinirole 24-hour prolonged release improves the quantity and quality of daily 'on' time
- Ropinirole prolonged-release tablets as adjunct therapy give 2.1 hours less awake time spent 'off' compared with baseline

■ 'Off' time ■ 'On' time with troublesome dyskinesia ■ 'On' time



- Once-daily ropinirole prolonged-release tablets provided significantly improved motor and Unified Parkinson's Disease Rating Scale activity of daily living score by -3.5 points compared with baseline after 24 weeks (p < 0.0001 vs. placebo)

LOCF = last observation carried forward

Source: Pahwa R, et al. *Neurology* 2007;68:1108–1115.

The EASE-PD Adjunct study showed that ropinirole 24-hour prolonged release significantly improved PD symptoms compared with placebo in patients not optimally controlled with levodopa, said Prof. Stocchi in his concluding remarks. This was seen alongside a significant reduction in the adjunct levodopa dose in the ropinirole group compared with the placebo group.

Management of Parkinson's disease: improving patient outcomes

Several studies have suggested that using dopamine agonists as an initial monotherapy, then adding levodopa when necessary,

may reduce the risk of patients developing dyskinesia compared with initiating levodopa therapy alone [3,4]. Animal studies have suggested that levodopa may have a ‘priming’ effect for dyskinesia: monkey models given levodopa rapidly develop dyskinesia, whereas they do not get dyskinesia when given a long-acting dopamine agonist. However, if the monkeys are exposed to levodopa before receiving the same dopamine agonists, they develop dyskinesias quickly. In humans this priming effect has never been adequately tested, so it is unclear whether adjunctive therapy with a dopamine agonist delays the onset of dyskinesia.

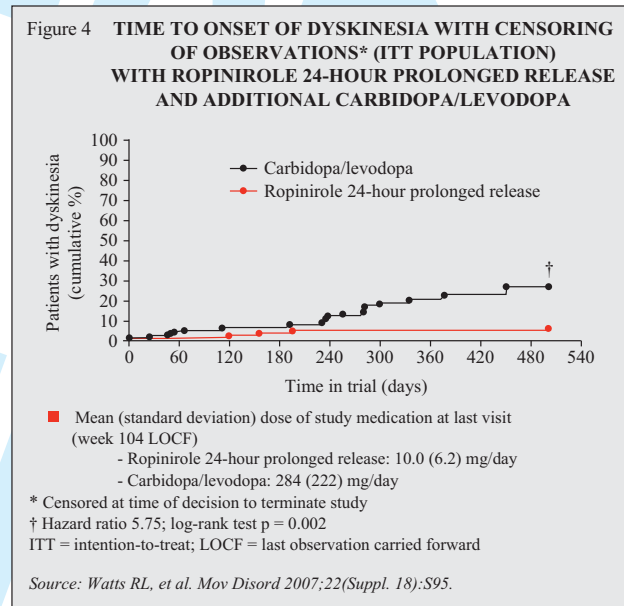
A phase III study (protocol 101468/228) evaluated the time to onset of dyskinesia during adjunctive treatment with ropinirole 24-hour prolonged release compared with additional carbidopa/levodopa in patients not optimally controlled with their existing levodopa dose [5]. The data were presented by Kapil D. Sethi (Department of Neurology, Medical College of Georgia, Augusta, GA, USA), who noted that this was the first study to evaluate the potential of a dopamine agonist to delay or prevent dyskinesia in adjunctive therapy.

This was a multicentre, double-blind, parallel-group study carried out in the United States, in which patients already receiving levodopa were randomised to receive adjunctive therapy with either ropinirole 24-hour prolonged release (2–24 mg/day) or additional carbidopa/levodopa of 50–1000 mg/day. Levodopa dose at baseline was 600 mg/day or less, and patients had been receiving levodopa for a maximum of three years. The permitted age range was 30–69 years. The primary outcome measure was time to onset of dyskinesia, and secondary end points included change from baseline in UPDRS activities of daily living (ADL) and total motor scores. The treatment phase was designed to last two years. However, the study was terminated early by the sponsor because of difficulty in recruiting enough patients who had been given initial therapy of levodopa rather than dopamine agonists, and subsequent changes in sample size requirements. The final intention to treat population was 104 patients in each arm.

Patients in the additional carbidopa/levodopa arm were significantly more likely to develop dyskinesia during the study period than patients on ropinirole 24-hour prolonged release (hazard ratio = 5.75, $p = 0.002$; Figure 4). The mean (standard deviation) dose of study medication at last visit (104 weeks or last observation carried forward) was 10.0 (6.2) mg/day of ropinirole and 284 (222) mg/day of carbidopa/levodopa. The statistical significance obtained despite the small sample size suggests a powerful benefit from adding a dopamine agonist once control with modest doses of levodopa becomes sub-optimal, Prof. Sethi observed. UPDRS motor and ADL scores were similar in the two groups, suggesting that the reduction in dyskinesia was not at the expense of motor control. There was no significant difference in adverse events [5].

Adjunctive therapy with once-daily ropinirole delayed the onset of dyskinesia compared with adjunctive carbidopa/levodopa in patients with mild-to-moderate PD

already treated with levodopa, the study concluded. Prof. Sethi said the study offered no evidence for a priming effect of levodopa in humans: dyskinesia can still be delayed in patients who have started on levodopa.



Dyskinesias have a profound effect on patients’ quality of life (QoL). Prof. Sethi presented QoL data from the EASE-PD Adjunct study described above [2]. The study recorded changes from baseline in the eight domains and summary index of the PDQ-39 QoL scale. In the placebo arm, QoL worsened in five of the eight domains during the study, whereas the ropinirole group saw statistically significant improvements in five of eight domains. At week 24 (or last observation carried forward), there was a mean difference of 3.4 points in the PDQ-39 summary index between the ropinirole and placebo groups, in favour of ropinirole (95% CI 1.4–5.5; $p = 0.001$).

Ropinirole 24-hour prolonged release can help address some of the problems faced by patients with PD, Prof. Sethi said in conclusion. Its benefits as an adjunctive therapy include reduced likelihood of developing motor complications, including dyskinesias, and improved quality of life. It enables levodopa dosage to be kept to a manageable level, thus reducing the risk of dyskinesia.

Practical considerations with ropinirole 24-hour prolonged release

Ropinirole immediate release has been used to treat PD for many years, and has proven efficacy in early and advanced PD, as well as a known tolerability profile. It can also delay the onset of dyskinesia when initiated as monotherapy [3]. It must be taken three times daily, with a daily dose of up to 24 mg/day. Symposium chairman Anthony H.V. Schapira (Department of Clinical Neurosciences, University College London, London, UK) summarised the key features of ropinirole 24-hour

prolonged release. It is a once-daily formulation with an advantageous pharmacokinetic profile that includes a steady rate of absorption and reduced fluctuations in plasma concentration. It has been shown to be noninferior to ropinirole immediate release as monotherapy^[1] and is also effective as adjunctive therapy^[2]. The dose range of up to 24 mg/day is maintained.

Ropinirole prolonged release is a faster and simpler dose titration regimen than ropinirole immediate release. This means that patients can reach an effective dose more rapidly and with good tolerance, Prof. Schapira noted. Studies have shown that patients already taking ropinirole immediate release can switch to an equivalent total daily dose of ropinirole overnight without significant change in their average daily exposure to ropinirole and without loss of efficacy. "This maintains motor control and simplifies scheduling for the patient," Prof. Schapira said.

Addressing patient concerns in PD

There is a high unmet need for better control of PD symptoms both during the day and at night. This was a key finding from the interim results of the Real Life, Real PD survey carried out

by the European Parkinson's Disease Association. So far, more than 1000 PD patients from 20 European countries have completed the online survey. Over two thirds of respondents said they did not feel in complete control of their symptoms over a 24-hour period. Forty-two per cent needed to plan their day around the times they take their medication. More than half have difficulty getting to sleep, and 72% wake at least once during the night. A quarter rated the quality of their sleep as poor or very poor.

Physicians tend to focus on motor symptoms, but nonmotor symptoms are equally concerning to patients, said Mary G. Baker, Chair of the WHO Working Group on Parkinson's Disease. Sleep problems, personality changes, and low mood all have a major effect on quality of life. Poor night-time symptom control can be a particular problem. Poor sleep can exacerbate fatigue and low mood, and often leads to disturbed sleep for the patient's partner. Wearing off at night interferes with patients' sex lives, stops them from turning during their sleep and causes difficulties with basic needs such as getting out of bed to urinate. Continuous delivery of ropinirole with ropinirole 24-hour prolonged release can effectively control symptoms during the day and night, with a positive impact on quality of life, said Prof. Stocchi.

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