Effect of Opicapone and Entacapone on Early Morning-OFF Pattern in Parkinson's Disease Patients with Motor Fluctuations

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Introduction

Levodopa still remains the most effective symptomatic treatment for Parkinson's disease (PD). However, following oral administration, levodopa is extensively metabolized in the periphery by dopa decarboxylase and catechol-O-methyltransferase (COMT).[1,2] Opicapone (OPC) is a third-generation, once-daily COMT inhibitor developed to fulfil the need for a more potent, longer-acting COMT inhibitor, with an improved safety profile.[1,2] OPC has been shown to be generally well tolerated and efficacious in reducing OFF-time in two large multinational trials in patients with PD and end-of-dose motor fluctuations (BIPARK-I and II).[3,4] Early-morning-OFF (EMO) periods in PD patients cause significant disability and have a negative impact on quality of life.[5]

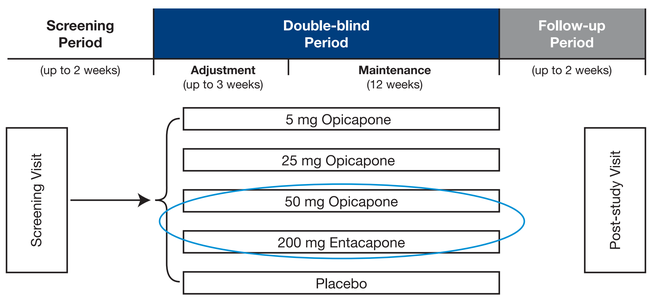
Objective

To evaluate the effect of OPC 50 mg versus entacapone (ENT) on EMO pattern.

Methods

BIPARK-I was a multinational, multicenter, double-blind, 14 to 15-week, placebo (PLC) and active-controlled study (**Figure 1**),[3] to evaluate the treatment effect of OPC in patients with PD and end-of-dose motor fluctuations. Eligible patients were male or female, aged 30–83 years, with a ≥3-year diagnosis of idiopathic PD, Hoehn and Yahr 1–3 at ON-state, receiving levodopa treatment for ≥1 year and experiencing end-of-dose motor fluctuations. The primary efficacy endpoint was the change from baseline in absolute OFF-time, based on patient diaries. In this *post-hoc* analysis, home-diary data from patients with wearing-OFF treated with OPC 50 mg or ENT were analyzed. Patients' 24-h diary data were stratified per daily hour. Asleep and ON/OFF fluctuations were characterized and depicted by daily hour. The proportion of patients who woke up in ON-/OFF-status and time-to-ON from first morning levodopa intake after wake-up were analyzed after a continuous period of ≥4 hours of sleep. EMO pattern was defined as the morning period for which the percentage of asleep-time per hour was over 5% (therefore not negligible) but below 50%, and also less than the percentage of OFF-time per hour.

Figure 1. Study design



Results

Patient population

- A total of 238 patients were randomized to receive treatment with OPC 50 mg (n=116) and ENT (n=122) in BIPARK-I
  - Full Analysis Set (defined as all randomized patients who took at least one dose of study medication and had at least one OFF-time assessment after baseline) comprised 235 patients (OPC 50 mg, n=115; ENT, n=120)
- Baseline demographic and disease characteristics were generally comparable between treatment groups (**Table 1**)

Table 1. Baseline characteristics (Full Analysis Set)

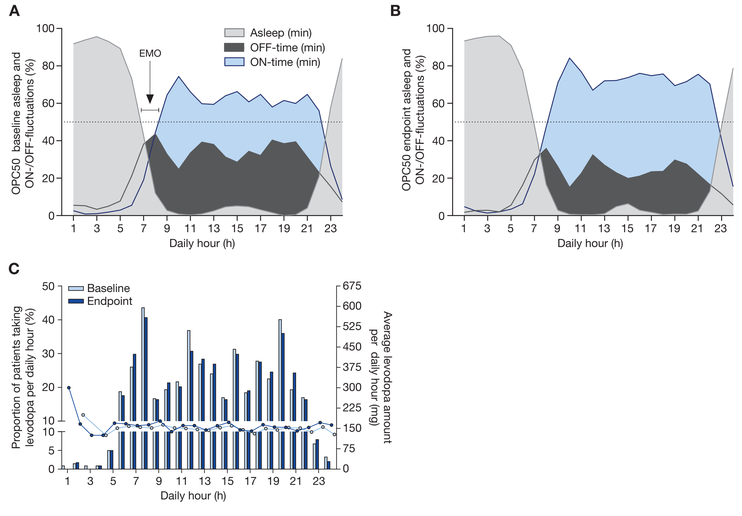
Characteristic	OPC 50 mg N=115	ENT N=120
Age, mean (years)	63.5	63.6
Gender – male, n (%)	69 (60.0)	74 (61.7)
Race – Caucasian, n (%)	115 (100)	120 (100)
Weight, mean (kg)	76.2	76.7
Height, mean (cm)	167.7	167.7
Body mass index, mean (kg/m^2)	27.1	27.2
Disease duration, mean (years)	7.0	7.1
Daily OFF-time, mean (hours)	6.2	6.5
Levodopa dose, mean (mg/day)	695.2	645.2

ENT, entacapone; OPC, opicapone

Analysis of EMO pattern

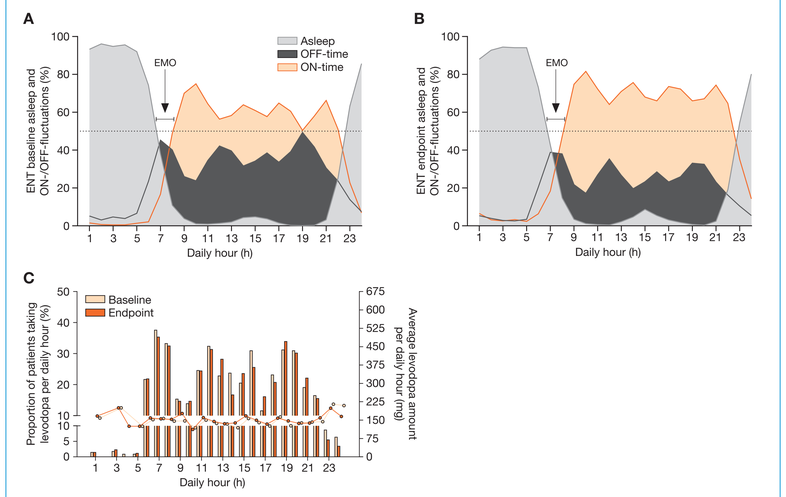
- For both treatments, at baseline and endpoint, the majority of asleep-time (>50%/h) was within 11pm to 6am (**Figures 2A, 2B, 3A and 3B**) and the proportions of patients taking levodopa per daily-hour were comparable (**Figures 2C and 3C**)
- Asleep-time was considered negligible (<5%/h) from 9am–9pm (**Figures 2A, 2B, 3A and 3B**)
- At baseline, <15% of patients woke up in ON-status, time-to-ON was >1h and EMO pattern was found to be between 6am to 8am (**Figures 2A and 3A**)
- At endpoint, for OPC 50 mg, the proportion of patients who woke up in ON-status increased by 12.2% from baseline, in comparison with 7.5% for ENT
  - For patients treated with OPC 50 mg, time-to-ON decreased by 17.7%, in comparison with 1.9% for ENT
- As reduction of morning OFF-time (%/h) was two-fold greater for OPC 50 mg versus ENT (20% vs 10%), no EMO was observed for OPC 50 mg, but EMO was still observed for ENT (**Figures 2B and 3B**)

Figure 2. PD patients' daily profile for OPC 50 mg: (A) asleep-time and ON/OFF profile at baseline, (B) asleep-time and ON/OFF profile at endpoint, and (C) pattern of levodopa therapy



EMO, early morning-OFF; OPC50, opicapone 50 mg; PD, Parkinson's disease

Figure 3. PD patients' daily profile for ENT 200 mg: (A) asleep-time and ON/OFF profile at baseline, (B) asleep-time and ON/OFF profile at endpoint, and (C) pattern of levodopa therapy



EMO, early morning-OFF; ENT, entacapone; PD, Parkinson's disease

CONCLUSION

In this *post-hoc* analysis of BIPARK-I, treatment with OPC, in comparison with ENT, led to a greater increase in the proportion of patients who woke up in ON-status and a greater decrease in time-to-ON from first morning levodopa intake. In addition, due to a substantial reduction in morning OFF-time, no EMO pattern was found for patients treated with OPC, in contrast to ENT.

References

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