ORIGINAL ARTICLE

Continuous intrajejunal levodopa-carbidopa intestinal gel in the treatment of patients with advanced Parkinson's disease – effects on motor symptoms

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Abstract

OBJECTIVES: Levodopa is the gold standard of Parkinson's disease (PD) treatment, but is often associated with disabling motor complications in patients with advanced PD. Levodopa/carbidopa intestinal gel (LCIG) infusion has been proved be beneficial on motor complications in the short-term as well as in long-term follow-up. Therefore is becoming an established therapeutic option for advanced PD patients with motor fluctuating symptoms unresponsive to conventional treatment. The aim of our study was to evaluate the impact of LCIG treatment to motor fluctuations.
METHODS: The assessments (performed at baseline and at a follow-up visit after PEG/J procedure using UPDRS IV, MDS-UPDRS scales) were realised in 21 patients with advanced stages of PD to analyse the LCIG efficacy in motor complications.
RESULTS: LCIG has demonstrated efficacy in reducing motor complications in advanced PD patients. A notable reduction of "OFF" time ($p<0.0001$) and "ON" time with dyskinesias ($p=0.007$) was observed in treated patients. Simultaneously, improvement of the functional severity of dyskinesias was achieved ($p=0.02$). The significant improvement of motor scores (UPDRS part III) in LCIG patients was estimated as well.
CONCLUSON: LCIG has demonstrated efficacy in reducing levodopa-associated motor complications in patients with advanced PD as well as improvement of motor functions evaluated by using UPDRS scores. LCIG is a useful treatment alternative recommended for patients with motor fluctuations and dyskinesias inadequately responding to traditional peroral medication.

Abbreviations:
Parkinson's disease (PD); Levodopa (L-Dopa); Levodopa/carbidopa intestinal gel (LCIG); percutaneous endoscopic gastrojejunostomy (PEG/J); The Unified Parkinson´s Disease Rating Scale (UPDRS); Movement Disorders Society – sponsored revision of the Unified Parkinson´s Disease Rating Scale (MDS-UPDRS)

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder (Wirdefeldt *et al* 2011). Pathologically is characterized by progressive degeneration and loss of the dopaminergic neurons in the substantia nigra pars compacta with subsequential deficit of dopamine. Clinically, PD includes motor symptoms such bradykinesia, rigidity, tremor, and postural instability as well as non-motor symptoms of autonomic dysfunction, sensory disturbances, mood disturbance and cognitive impairment. (Aarsland *et al* 2003). Dopamine replacement with levodopa was first shown to reduce clinical symptoms of PD in the 1960s (Yahr *et al* 1969) and since then has remained the mainstay in the treatment of PD (Hauser 2009; Olanow *et al* 2004). While the majority of PD patients initially respond positively to conventional dopaminergic medication, during the disease progression and chronic L-dopa treatment, disabling mainly motor complications, including "OFF" periods (state of poor mobility and stiffness), "ON-OFF" phenomenon (unpredictable swing from mobility to immobility) and L-dopa-induced dyskinesias occur in most PD patients especially in advanced stages (Ahlskog & Muenter 2001). The mechanism is not sufficiently elucidated, but is presumably caused by the ongoing neurodegeneration and chronic medical use, especially the higher dosage and longer duration of levodopa treatment (Grandas *et al* 1999). In patients with advanced Parkinson's disease, provision of a dose of L-dopa that effectively controls "OFF" time without inducing dyskinesia can be difficult. Clinical and laboratory evidence suggests that L-dopa-induced motor complications are related to the nonphysiological restoration of brain dopamine (Olanow *et al* 2006). The intermittent administration of oral levodopa, erratic gastric emptying, variable jejunal absorption, and the short half-life of L-Dopa (60–90 min) leads to the plasmatic fluctuation of L-dopa level (Nutt *et al* 1994; Hardoff *et al* 2001). This variability in plasma and subsequently striatal dopamine concentrations of levodopa result to nonphysiological and pulsatile stimulation of dopamine receptors thus underlying molecular and neuropatological changes in striatal neurons resulting into the development of motor complications (Miller & Abercrombie1999; Bibbiani *et al* 2005; de la Fuente *et al* 2004; Olanow *et al* 2006). On this basis, a major goal of PD treatment options in the recent years has been the development of an approach that offers more continuous dopaminergic stimulation thus provides clinical benefit as well as decreases the risk of development of motor fluctuations and dyskinesias.

Levodopa–carbidopa intestinal gel (LCIG) was developed to overcome the limitation of oral treatment. The LCIG system consists of a levodopa/carbidopa-gel formulation delivered directly to the proximal jejunum via a percutaneous endoscopic gastrojejunostomy (PEG/J) tube connected to a portable infusion pump (Nyholm *et al* 2004, 2005). Infusion of LCIG bypasses gastric emptying, thereby avoiding the fluctuation in plasma levodopa levels and providing more stable plasma L-dopa levels than oral formulations (Nyholm *et al* 2003, 2013). Several open-label studies have shown a significant reduction in "OFF"-time and dyskinesia severity in advanced PD as compared to standard oral treatment (Table 1) (Nyholm *et al* 2005; Stocchi *et al* 2005; Antonini *et al* 2007, 2008, 2015; Eggert *et al* 2008; Puente *et al* 2010; Olanow *et al* 2014; Slevin *et al* 2015). Furthermore LCIG has demonstrated beneficial effect on non-motor symptoms (Olanow *et al* 2014; Honig *et al* 2009) as well as quality of life (QoL) (Fasano *et al* 2012; Zibetti *et al* 2013; Olanow *et al* 2014). Despite of the limited number of double-blind controlled trials, a levodopa-carbidopa intestinal gel is approved for medical use in 44 countries.

METHODS

Patients
The study comprised patients with a diagnosis of idiopathic Parkinson´s disease (according to the United Kingdom Brain Bank criteria) who started LCIG treat-

Tab. 1. Effect of LCIG on "OFF" time and troublesome dyskinesia.

	Change in motor state				
Study	**Funtional "ON" time**	**"Off" (%)**	**Dyskinesia (%)**	**Patients**	**Duration**
Nyholm *et al* (2005)	+16	–17	+2	24	3 weeks
Stocchi *et al* (2005)		–70		6	6 m
Antonini *et al* (2007)	+42	–28	–13	7	12 m
Eggert *et al* (2008)	+51	–39	–12	13	12 m
Antonini *et al* (2008)		–46	–32	22	24 m
Puente *et al* (2010)	+40	–66		9	18 m
Olanow *et al* (2014)	+47	–50	–4h	71	12 weeks
Antonini *et al* (2015)		–66	–32	172	12 m
Slevin *et al* (2015)	+50	–50	–2h	66	52 weeks

ment in 2nd Department of Neurology, Comenius University, Bratislava between 2009 and 2014. All patients had received long-term L-dopa treatment and displayed significant motor fluctuations inadequately responding to oral PD medication. Evidence of a satisfactory therapeutic effect of LCIG before performing PEG/J procedure was required. A therapeutic effect was defined as at least 50% improvement of motor state (evaluated by UPDRS part. III) during LCIG treatment in "ON" state compared to "OFF" state. This evidence is assessed during the „titration phase"(endoscopy-assisted nasointestinal tube placement) which requires a hospital stay for 3–4 days. After the evidence of the LCIG efficiency, patients returned home with their previous oral treatments, and waited for the approval of reimbursement by their health insurance company. When the treatment was granted, patients were admitted to the hospital for the internalization of the PEG/J tube (LCIG procedure). Subject consent was obtained in agreement with the Declaration of Helsinki and an informed consent regarding endoscopy procedure, PEG/J tube and NJ tube placement from all patients is available.

LCIG procedure

Patients were switched from the conventional therapy to LCIG (contains 20 mg/mL levodopa and 5 mg/mL carbidopa) supplied in cassettes containing 100 mL of gel solution (Duodopa intestinal gel, Abbvie Laboratories) connected with a portable infusion pump (CADD-Legacy® Duodopa, Smiths Medical). Initially, each patient had a nasojejunal (NJ) tube (Stabilife Ch10 nasointestinal tube) inserted under endoscopic visualisation to evaluate the clinical response to LCIG. All oral PD medications were stopped 5 hours prior to NJ tube placement during this period except for the use of oral L-dopa (immediate-release tablets) that could be taken at bedtime when the pump was turned off. The dose of LCIG required to optimise PD control was titrated individually over the first 3 consecutive days (15 h/day – 07:00–22:00). The initial titration doses were calculated from the previous oral PD medication according to the levodopa equivalent daily dose (Tomlinson *et al* 2010). The total daily dosage of LCIG was composed of a morning bolus dose; the continuous dose and the extra bolus doses given as required based on patient's symptoms. The effective doses were further modified individually until achieving the maximal motor performance without clinically relevant dyskinesias. After completion of the titration phase and a clear clinical improvement, patients were re-initiated to the previous oral medication and demitted. After approval of treatment reimbursement from their health companies, patients were readmitted to the hospital for PEG tube placement (Freka® PEG Set Gastric FR 15 / 20 and Freka® Intestinal Tube FR 9 for PEG 15 / 20) for long-term administration.

Clinical evaluation

Patients were assessed at a baseline before the internalisation of LCIG after a 6–8 month period of continuous treatment. The first baseline evaluation was performed during the hospitalisation preceding the PEG/J procedure. The assessments were realised after overnight withdrawal of antiparkinsonian medication ("OFF" state), and 30–60 minutes after administration of peroral treatment – "ON" state. All assessments were performed as part of routine clinical practice. Baseline assessments included: UPDRS (part III – motor functions, part IV – complication of therapy), MDS-UPDRS scale (Goetz *et al* 2008), Hoehn-Yahr staging scale (HY) (Hoehn & Yahr 1967). All baseline assessments were performed during conventional L-dopa treatment in "ON" state. UPDRS part III was also assessed in "OFF" state. After placement of percutaneous endoscopic gastrostomy (PEG/J), follow-up visits were performed to optimize LCIG dose and to evaluate efficacy of the treatment. Efficacy was evaluated using MDS-UPDRS, UPDRS III and UPDRS IV during "ON" state.

Statistics

Descriptive statistics were calculated for each observed group. For all analyses, "baseline" is defined as the last available data collected prior to PEG/J-tube insertion. Within groups, change from baseline to follow up visit was assessed with using of one-sample *t*-test. All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL). $p < 0.05$ were considered significant.

RESULTS

Patient's characteristics

Our study comprised of 21 patients with Parkinson´s disease (10 women, 11 men, ratio 0.9) with the mean age of 69 years (59–74), a mean age of 57 years at PD onset, and mean disease duration of 16 years. The demographic and baseline clinical data are displayed in Table 2.

Motor outcome

At baseline, patients had a mean (± SD) "OFF" time of 5.8 (± 1.6) h/day and mean "OFF" time at the follow up visit was 2.7 (±1.1) h/day (significantly reduced

Tab. 2. Baseline clinical and demographic data.

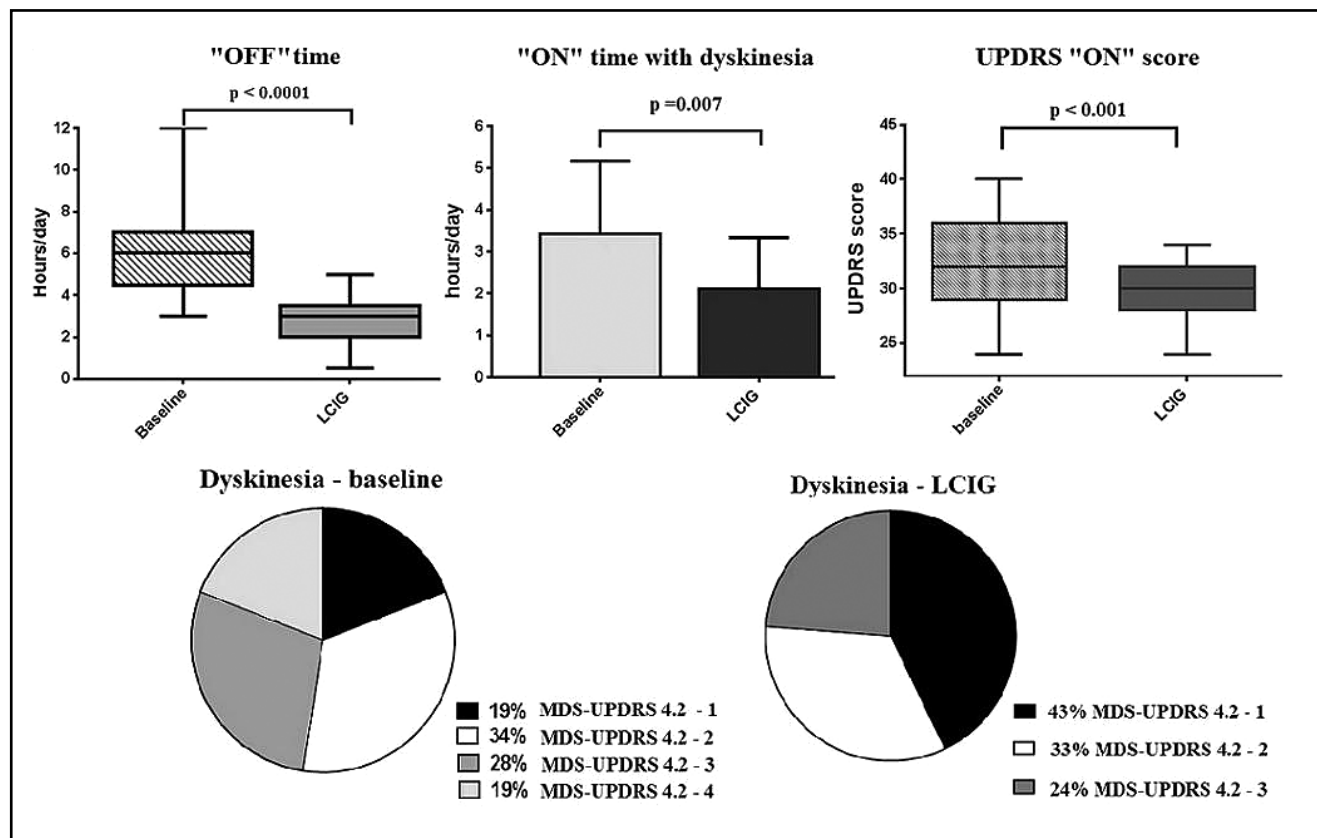|	
Gender Female/Male (n, %)	10(48%) / 11(52%)
Age (years)	69
(median range)	(59–74)
Age at PD onset (years)	57
(median range)	(40–63)
Duration of PD to LCIG treatment (years)	16
(median/range)	(6–25)
Hoehn and Yahr stage	3 (2.5–5)

Fig. 1. Motor symptoms in PD patients treated with LCIG (mean change from baseline to follow up).

Tab. 3. Clinical PD data at baseline and after LCIG treatment.

PD symptoms	baseline	LCIG	*p*-value
"OFF" time (MDS-UPDRS 4.3) hours/day (mean/SD/range)	5.8 (±1.6) (3–12)	2.7 (±1.1) (0.5–4)	<0.001
''ON'' time with dyskinesia (MDS-UPDRS 4.1) hours/day (mean/SD/range)	33 (±1.4) (1–8)	2.1 (±1.2) (0–5)	0.007
Dyskinesia dysability (MDS-UPDRS 4.2) 1,2,3,4 (%)	19/34/28/19	43/33/24/0	0.02
UPDRS motor score in "ON" state (mean/SD/range)	32 (±4.8) (24–40)	30 (±8.3) (24–38)	<0.001

($p<0.0001$ versus baseline) (Table 3, Figure 1). Similarly, "ON" time with dyskinesia at follow-up visit reaches the mean value of 2.1 (±1.2) h/day, thus a significant improvement was estimated in comparison to baseline 3.3 (±1.4) h/day ($p=0.007$) (Table 3, Figure 1). "ON" time spent with troublesome dyskinesias (UPDRS part IV, item 33, MDS-UPDRS 4.2–3 and 4) was significantly reduced from 1.8 (± 1.2) h/day at baseline to 1.0 (±0.7) h/day ($p=0.02$) (Table 3, Figure 1). The improvement of the functional impact of dyskinesias was achieved as well. 14% of patients with LCIG treatment exhibited no dyskinesias during the day. Simultaneously, none of the patients in the follow-up visit exhibited disabling dyskinesias (MDS-UPDRS part 4.2–4), as was observed at baseline by 19 % of patients. In general, dyskinesias duration was reduced by 36 % ($p=0.007$), dyskinesias disability by 44% ($p=0.02$), and OFF duration by 53% ($p<0.0001$). Motor condition evaluated by

the motor section (UPDRS part III) was significantly improved as compared to pre-LCIG treatment conditions as well ($p<0.001$) (Table 3, Figure 1).

Discussion

In our study, we assesed the effect of the continuous dopaminergic stimulation (provided by LCIG) on motor symptoms. This analysis confirms significant improvements on motor complications similar to previously published LCIG – studies (Table 1) (Nyholm *et al* 2005; Stocchi *et al* 2005; Antonini *et al* 2007, 2008, 2015; Eggert *et al* 2008; Puente *et al* 2010; Zibetti *et al* 2013; Olanow *et al* 2014; Slevin *et al* 2015). Specifically, there was a significant reduction in total daily "OFF'" time as recorded via the UPDRS (part IV. item 39) and MDS-UPDRS (part 4.3). Whereas the original UPDRS (part IV item 39) is based on the percentage of daily "OFF"

time in 25% increments, use of the MDS-UPDRS provided more accurate data regarding wake time reported as daily "OFF" hours (Goetz *et al* 2008). The average reduction of "OFF" time in our study is similar to the results of "OFF" – time reduction documented in the double-blind, double-dummy trials (Olanow *et al* 2013; Antonini *et al* 2015). We have also reported significant reductions of "ON" time dyskinesias (36%) as well as improvement of dyskinesia severity which is consistent with previous open-label studies (Antonini *et al* 2008, 2015; Eggert *et al* 2008). There was a significant reduction of troublesome dyskinesias (severity 3 and 4) in treated patients in comparison to the baseline data. The reduction in the severity of dyskinesia (non-troublesome vs. troublesome) was more prominent as compared to the decrease in the duration of dyskinesias. A complete elimination of functionally disabling troublesome dyskinesias (MDS-UPDRS part 4.2–4) in the follow up time was also achieved; this finding is in contrast with the results from the clinical study performed by Olanow *et al* (2014). The decrease in "OFF" time and increase in "ON" time without troublesome dyskinesia in the LCIG group was observed, while "ON" time with troublesome dyskinesias showed no significant change. Several previous, open-label studies had already evaluated LCIG during chronic treatment (Table 1) (Nyholm *et al* 2005; Stocchi *et al* 2005; Antonini *et al* 2007, 2008, 2015; Eggert *et al* 2008; Puente *et al* 2010; Olanow *et al* 2014; Slevin *et al* 2015). Although, differences in the study design limit any summarization of the numerical findings, measures of "OFF" time found significantly improved results in all studies as well as in majority of dyskinesias measures. In addition, a randomized crossover trial (Nyholm *et al* 2005) has compared individually optimized conventional treatment with 3 weeks of dummy nasoduodenal LCIG infusion (to blind the conventional therapies). The main outcome of this study was, that "ON" state was significantly greater during LCIG than during conventional therapy (at 90.7 vs. 74.5 %, respectively, *p*<0.01), and the mean duration of "OFF" state was significantly lower (*p*<0.01). For ratings of "ON" with moderate-to-severe dyskinesias, LCIG and conventional therapy showed no significant difference. We also observed an improvement of UPDRS part III in "ON" state after LCIG treatment. Consistently with our results, other clinical studies with LCIG also reported significant improvement of the UPDRS III scores (Nyholm *et al* 2008; Antonini *et al* 2008). It is not elucidated whether UPDRS III improvement is the result of continuous treatment, or improved mobility as a consequence of reduced dyskinesia severity and "OFF" time. Both factors may explain these improvements. In advanced PD continuous delivery seems to be a key factor in the management of motor fluctuations (Olanow *et al* 2014). Patients in the cohort described here also reported significant reductions in daily "ON"–time with dyskinesias and dyskinesia severity which is consistent with

previous open-label reports (Antonini *et al* 2008, 2012, 2015; Eggert *et al* 2008; Annic *et al* 2009). However, our study design limitation included a modest number of recruited patients. Despite of this fact our data are generally consistent with the results obtained in several randomized, controlled trials of LCIG.

Financial disclosure/conflict of interest concerning the research related to the manuscript

I certify that all my affiliations (relationships) with or financial involvement (consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties) with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed below. Dr. Gmitterova and Dr. Minar have received a travel grant and honoraria for consulting services from Abbvie.

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