

C A S E R E P O R T

Continuous dopaminergic stimulation in a patient treated with daytime Levodopa-carbidopa intestinal gel and overnight Rotigotine: a case report

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Summary. Patients with Parkinson's disease (PD) receiving long-term L-Dopa therapy eventually develop motor complications with unpredictable "on-off" response fluctuations and involuntary movements, leading to progressive disability. Hence, the search for alternative therapeutic choices based on continuous dopaminergic stimulation (CDS) becomes crucial for the treatment of advanced PD. Here, we describe the case of a 70-year-old man with a 9-year history of PD, treated with daytime levodopa-carbidopa intestinal gel (LCIG) and overnight Rotigotine transdermal patch. LCIG monotherapy significantly reduced motor fluctuations and prevented the appearance of unpredictable off periods; concurrently, overnight Rotigotine improved his sleep quality and morning akinesia. Both LCIG and Rotigotine induce CDS, which conceptually mimics physiologic striatal dopamine receptor function. Hence, they both represent a good therapeutic option for the treatment of advanced PD. (www.actabiomedica.it)

Key words: Parkinson's disease, Continuous dopaminergic stimulation, levodopa/carbidopa intestinal gel infusion, Rotigotine, motor fluctuations, morning akinesia

Background

Parkinson's disease (PD) is characterized by a progressive degeneration of dopaminergic neurons with subsequent reduction of striatal dopamine level. In physiological conditions, dopamine neurons have relatively constant rates of tonic activity, exposing striatal dopamine receptors to constant levels of dopamine (1). Disease progression leads to fewer remaining striatal dopamine terminals and consequently decreased capacity to buffer fluctuations in dopamine levels. Patients with PD receiving long-term L-Dopa therapy eventually develop motor complications with unpredictable "on-off" response fluctuations and involuntary movements, leading to progressive disability (2, 3). The development of motor complications has been linked to intermittent stimulation of dopamine receptors and consequent alterations in neuronal firing patterns (4).

Consequently, the search for alternative therapeutic choices based on continuous dopaminergic stimulation (CDS) becomes crucial for the treatment of advanced PD and the reduction of long-term complications.

Case

The patient was a 70-year-old man with a 9-year history of Parkinson's disease, started with diffuse bradykinesia and postural instability. In his past medical history, he suffered from impaired glucose tolerance, hypertension, dyslipidemia and Obstructive Sleep Apnea Syndrome. Moreover, he was treated with prophylactic antiepileptic therapy (Phenobarbital 50 mg/day) for a meningioma of left temporal lobe.

About 5 years after onset of PD, he started to present motor fluctuations with wearing-off symptoms,

progressively worsened by the appearance of unpredictable and sudden off periods. The clinical worsening also included camptocormia and paroxysmal freezing of gait with frequent fallings. Moreover, he complained about insomnia secondary to nocturnal hypokinesia with difficulty in turning in bed, night-time leg cramps and morning akinesia. With the passing of time, all these symptoms became poorly controlled on oral dopaminergic therapy.

For this reason, he was admitted to our Neurological Department as a suitable candidate for Levodopa-carbidopa intestinal gel (LCIG) treatment. He underwent naso-intestinal evaluation with LCIG (Duodopa®-gel) followed by permanent treatment with LCIG via percutaneous endoscopic gastrostomy and jejunal tube (PEG/J).

The assessments, performed at baseline and at follow-up visits, included: Unified Parkinson's Disease Rating Scale, motor fluctuation data obtained from patients diaries ("on" without dyskinesia, "on" with dyskinesia, and "off"), PDQ-39 Questionnaire, PD Sleep Scale-2 (PDSS-2) and Epworth Sleepiness Scale (ESS).

Prior to LCIG treatment, daily oral dopaminergic medication consisted of Rotigotine transdermal patch (4 mg/day, administered from 8:00 a.m. to 8:00 p.m.), Rasagiline (1 mg/day), melevodopa/carbidopa (Sirio®, 500 mg/day, administered five times daily) and two tablets of slow-release levodopa/benserazide (Madopar HBS®, 100/25 mg, administered at 10:00 p.m.).

After PEG/J placement, all oral levodopa therapy was interrupted, including evening therapy with levodopa/benserazide.

LCIG monotherapy (total daily dose: 1080 mg, administered from 7:00 a.m. to 10:00 p.m.) significantly reduced motor fluctuations and akinesia (by approximately 60%), allowing him to walk longer distances, and with partial effectiveness on paroxysmal freezing and camptocormia (Fig. 1, 2). During follow-up visits, the parameters of LCIG continuous infusion were gradually reduced to 870 mg daily because of the appearance of axial dyskinesias.

For the treatment of nocturnal disturbances, the administration of Rotigotine was shifted from daytime to overnight (from 10:00 p.m. to 7:00 a.m.), when the patient was not receiving LCIG treatment. After that,

he reported an improvement of night's sleep, with better movement fluency and disappearance of morning akinesia. The assessments showed a reduced diurnal hypersomnolence and, consequently, an improved global quality of life (Fig. 1).

Discussion

Both Levodopa-carbidopa intestinal gel and Rotigotine transdermal patch have the potential to induce continuous dopaminergic stimulation, which conceptually more closely mimics physiologic striatal dopamine receptor function, clarifying the efficacy of both treatments respectively on motor fluctuations and sleep quality.

Before receiving LCIG treatment, the patient presented the typical motor complications of chronic levodopa therapy, with both predictable and unpredictable off periods. After PEG/J placement, a significant clinical improvement was observed, with benefit in motor fluctuations and gait.

LCIG consists of a continuous infusion of a gel form of Levodopa-carbidopa, which is directly delivered into the small intestine, where most of the absorption of levodopa takes place. Moreover, this administration has the advantage of bypassing the stomach, avoiding delayed absorption of levodopa related to delayed and erratic gastric emptying. In this way, it provides continuous delivery of levodopa so that plasma concentrations of the drug can be kept near constant. For this reason, it represents a good therapeutic option for the treatment of advanced PD (5, 6).

Rotigotine is a high-potency agonist at dopamine D₁, D₂ and D₃ receptors (7), effective as an alterna-

	Pre-CDS treatment	3 months after CDS treatment	6 months after CDS treatment
UPDRS-Part II	"off": 20	10	10
	"on": 11		
UPDRS-Part III	"off": 36	18	18
	"on": 19		
PDQ-39	70	52	52
PDSS-2	21	9	9
ESS	12	8	8

Figure 1.

Time	Sleep	OFF	ON	ON slight dyskinesia	ON severe dyskinesia
06:00	x				
06:30	x				
07:00		x			
07:30		x			
08:00		x			
08:30			x		
09:00			x		
09:30			x		
10:00		x			
10:30		x			
11:00		x			
11:30			x		
12:00			x		
12:30			x		
13:00		x			
13:30		x			
14:00		x			
14:30		x			
15:00			x		
15:30			x		
16:00			x		
16:30		x			
17:00		x			
17:30			x		
18:00			x		
19:00		x			
19:30		x			
20:00		x			
20:30			x		
21:00			x		
21:30			x		
22:00		x			
22:30		x			
23:00			x		
23:30			x		
00:00			x		
00:30			x		
01:00	x				
01:30	x				
02:00	x				
02:30	x				
03:00		x			
03:30		x			
04:00		x			
04:30	x				
05:00	x				
05:30	x				

Figure 2. a) Patient diary pre-CDS treatment

Time	Sleep	OFF	ON	ON slight dyskinesia	ON severe dyskinesia
06:00	x				
06:30	x				
07:00		x			
07:30			x		
08:00			x		
08:30					x
09:00					x
09:30					x
10:00					x
10:30				x	
11:00				x	
11:30				x	
12:00				x	
12:30				x	
13:00				x	
13:30				x	
14:00				x	
14:30				x	
15:00				x	
15:30			x		
16:00			x		
16:30			x		
17:00				x	
17:30				x	
18:00				x	
19:00			x		
19:30			x		
20:00			x		
20:30			x		
21:00			x		
21:30			x		
22:00			x		
22:30			x		
23:00			x		
23:30			x		
00:00	x				
00:30	x				
01:00	x				
01:30	x				
02:00	x				
02:30	x				
03:00	x				
03:30	x				
04:00	x				
04:30	x				
05:00	x				
05:30	x				

Figure 2. b) Patient diary 3 months after CDS-treatment

Time	Sleep	OFF	ON	ON slight dyskinesia	ON severe dyskinesia
06:00	x				
06:30	x				
07:00		x			
07:30			x		
08:00			x		
08:30				x	
09:00				x	
09:30				x	
10:00				x	
10:30				x	
11:00				x	
11:30				x	
12:00				x	
12:30				x	
13:00				x	
13:30				x	
14:00				x	
14:30				x	
15:00				x	
15:30			x		
16:00			x		
16:30			x		
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22:00			x		
22:30			x		
23:00			x		
23:30			x		
00:00	x				
00:30	x				
01:00	x				
01:30	x				
02:00	x				
02:30	x				
03:00	x				
03:30	x				
04:00	x				
04:30	x				
05:00	x				
05:30	x				

Figure 2. c) Patient diary 6 months after CDS-treatment

tive therapeutic option in both early and advanced Parkinson's disease. Transdermal application avoids fluctuating gastrointestinal absorption due to delayed gastric emptying and first-pass metabolism, allowing for continuous, once-daily administration. Besides, the continuous release of rotigotine from the transdermal delivery system gives stable plasma drug concentration over 24 hours leading to continuous receptor stimulation, which reflects the normal physiological state in which dopaminergic receptors function (8, 9). The clinical studies of Rotigotine in patients with early- and advanced-stage PD demonstrate that transdermal application effectively reduces the cardinal motor symptoms of the disease and improves early-morning motor symptoms (10). Moreover, other studies support the hypothesis that nocturnal disturbances can arise as a consequence of inadequate nighttime dopaminergic stimulation, which could potentially be alleviated by CDS (11). It is known that oral sustained-release formulation of levodopa have a half-life of 3–6 hours (12); for this reason, we preferred to stop the administration of levodopa evening therapy in favour of the overnight switch to Rotigotine, which seems to be convenient, well tolerated and effective for the treatment of nocturnal and early morning disabilities in PD patients. In our opinion, this could be a good strategic alternative to nocturnal LCIG infusion, which is reserved for more severe cases of nocturnal akinesia.

Furthermore, daily LCIG treatment itself could have contributed to the improvement of sleep quality observed, as previously reported in other clinical trials (13).

Continuous dopaminergic stimulation represents a therapeutic strategy for the management of Parkinson's disease, allowing amelioration of levodopa-related motor complications and avoiding fluctuations in dopamine levels related to intermittent oral levodopa.

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