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BRIEF COMMUNICATION

Levodopa–carbidopa intrajejunal gel in advanced Parkinson disease with "on" freezing of gait

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Abstract Freezing of gait is a common and disabling disorder in advanced Parkinson's disease (PD). The relationship with dopaminergic medication is complex and often non-linear, thus freezing may occur even when the core parkinsonian features (tremor, rigidity and bradykinesia) appear optimally controlled. We evaluated the effect of Levodopa–carbidopa intrajejunal gel in a group of seven non-demented PD patients with prominent episodes of freezing refractory to adjustments of oral therapy. Clinical assessments were performed in the best "on" state before starting Levodopa–carbidopa intrajejunal gel, while patients were on their standard oral Levodopa (O-LD), and infusion treatment. The main outcome measures were change in freezing of gait (FOG) Questionnaire and UPDRS motor score. FOG Questionnaire and UPDRS subscores related to gait and postural stability significantly improved during Levodopa–carbidopa intrajejunal gel infusion in all patients compared to O-LD treatment. In four out of seven patients, the Levodopa–carbidopa intrajejunal gel dose was equivalent or slightly higher but in three patients was lower compared to O-LD dose recorded at baseline visit. In selected patients, Levodopa–carbidopa intrajejunal gel may improve freezing refractory to oral dopaminergic therapy.

Keywords Advanced Parkinson's disease · Freezing · Duodenal levodopa–carbidopa infusion

Background

Freezing of gait (FOG) and gait difficulties are common and disabling disorders in advanced Parkinson's disease (PD) [1].

Although the pathophysiology of FOG remains poorly understood, dopaminergic and non-dopaminergic pathways are implicated [2–5]. The relationship between FOG and dopaminergic medications is not fully predictable. The spectrum of response ranges from the "Off"-FOG, which is a common manifestation of motor fluctuations associated with low dopaminergic drive and relieved by dopaminergic therapy, and "On"-FOG, which appears under the effect of medications and in some case is even worsened by their administration [6]. There are different types of "On" FOG: (1) "pseudo-on" FOG, occurring during a seemingly optimal "on" state, (2) "drug-refractory" FOG, which is indifferent to changes in dopaminergic medication and (3) "true-on" FOG, which occurs or worsens in the "on" state and may improve after therapy reduction [7].

We evaluated the effectiveness of Levodopa–carbidopa intrajejunal gel (LCIG) in seven non-demented PD patients with prominent episodes of freezing refractory to adjustments of oral therapy.

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Patients and methods

Screening the charts of 75 PD patients treated with LCIG at three Italian Movement Disorders centers (Cagliari, Milan, Venice), we identified 7 patients (Table 1) who presented On-FOG before switching from oral Levodopa (O-LD) to LCIG therapy. All patients screened met the PD UK Brain Bank criteria [8] and had shown a sustained response to dopaminergic treatment over the years, with motor fluctuations and/or dyskinesias. None of the patients had significant cognitive impairment (MMSE <24, FAB <13), psychiatric or severe systemic illnesses.

Assessment of PD disability

The main outcome measures were the UPDRS II and III scores and the FOG Questionnaire (FOGQ).

We also extrapolated and collated the gait and postural stability-specific subscores of UPDRS II (items 13–14–15) and III (items 29–30). Dyskinesias presence and duration were assessed by UPDRS scale item 32.

Levodopa dose (LDD) and Levodopa equivalent dose (LED, including LDD + all antiparkinsonian therapies, such as dopamine agonists, rasagiline, I-COMT) was calculated for each patient during O-LD and LCIG treatment (Table 2).

Evaluations were performed in "ON" state either during oral LD (O-LD-ON) (60–90 min after intake of usual morning LD dose) and LCIG (LCIG-ON) (60–90 min after starting LCIG infusion).

FOGQ, based on patient and caregiver assessment, was used to assess the frequency and duration of freezing episodes in both O-LD (FOGQ-O-LD) and in LCIG treatment (FOGQ-LCIG).

Data analyses

The changes in the main outcome measures and in gait-related subscores of UPDRS II and III were analyzed with Wilcoxon test for repeated measures. Significance threshold was set at $p < 0.05$. Data were analyzed using the Statistical Package for the Social Sciences (version 19; SPSS Inc., Chicago, USA).

Results

Median PD and LCIG treatment duration and doses are reported in Tables 1 and 2.

UPDRS scores recorded under O-LD and LCIG treatment are reported in Fig. 1. All UPDRS subscores related to gait and postural stability significantly improved with LCIG in all patients compared to O-LD ($n = 7$, UPRDS II total $p = 0.018$; item 13 falling $p = 0.034$; item 14 freezing $p = 0.026$; item 15 walking $p = 0.026$; UPDRS III total $p = 0.027$; item 29 gait $p = 0.027$; item 30 postural stability $p = 0.025$). The improvement of item 32 dyskinesias was not significant ($p = 0.18$).

FOGQ significantly improved ($p = 0.017$ 45.1 %) on LCIG (FOGQ-O-LD 19 ± 1.4; LCIG: 10.4 ± 1.6).

Conclusion

Our results suggest that LCIG could be a useful therapeutic strategy in patients with FOG and gait disturbances refractory to oral therapy. Remarkably, FOGQ and the subscores of UPDRS II and III related to gait and postural stability improved in all patients selected after switching from O-LD to LCIG.

In 4 of our 7 patients, LED was increased after switching from oral therapy, while in 3 the total dopaminergic dose was reduced (Table 2).

We believe the first subgroup (see pt 1; video sections 1–2) represents a sample of "relatively undertreated" patients. In other words, the O-LD dose ensuring a relatively good control of rigidity, bradykinesia and tremor, is insufficient to improve gait disturbances, particularly

Table 1 Demographic and clinical characteristics of patients

Pt	Age at implant (years)	PD duration (years)	HY	Gender	LCIG (months)	MMSE	FAB
1	78	13	4	M	18	28	18
2	76	13	4	F	12	26	15
3	56	11	3	F	9	30	18
4	74	15	4	F	14	27	15
5	73	24	4	M	12	25.7	15
6	59	5	3	F	12	30	18
7	57	12	3	F	8	26.2	16

The median age was 73 years (25th percentile 57, 75th percentile 75), the median PD duration was 13 years (25th percentile 11, 75th percentile 15)

Table 2 Treatment taken by each patient at baseline (on oral levodopa) and during levodopa continuous intrajejunal gel infusion

Pt	Oral therapy				LCIG						
	LD	DAED	Entacapone ED	Oral LED	LD continuous infusion	LD morning dose	LD night dose	LD extra dose	Total LD	DAED	LCIG LED
1	1250	315	/	1565	1350	160	60	80	1650	105	1755
2	1200	210	160	1570	1080	150	60	40	1330	105	1435
3	600	315	/	915	570	140	60	60	830	/	830
4	500	105	150	755	675	160	60	50	945	/	945
5	900	160	270	1330	1440	140	60	/	1640	/	1640
6	600	210	/	810	720	140	60	/	920	105	1025
7	800	320	180	1300	720	120	60	50	950	200	1150

LD Levodopa dose, *DAED* equivalent dose of Dopamine agonists, *Entacapone ED* entacapone equivalent dose, *oral LED* levodopa equivalent dose (LD + DAED + entacapone ED). *Total LD* (continuous infusion+, morning dose + extra doses + the small extra dose provided during intestinal tube washing at nighttime), *LCIG LED* total LD + DAED

Equivalent dose for DA and entacapone have been calculated according to a published formula (Tomlinson et al.; Mov Disord. 2010; 25(15):2649–2653)

Median duration of LCIG treatment was 12 months (25th percentile 9, 75th percentile 14)

In 4 out of 7 pts (1–4–5–6: Subgroup 1) LD dose was equivalent or slightly increased after switching continuous infusion compared to the dose of oral LD, while in three patients (2, 3, 7: Subgroup 2) it was reduced

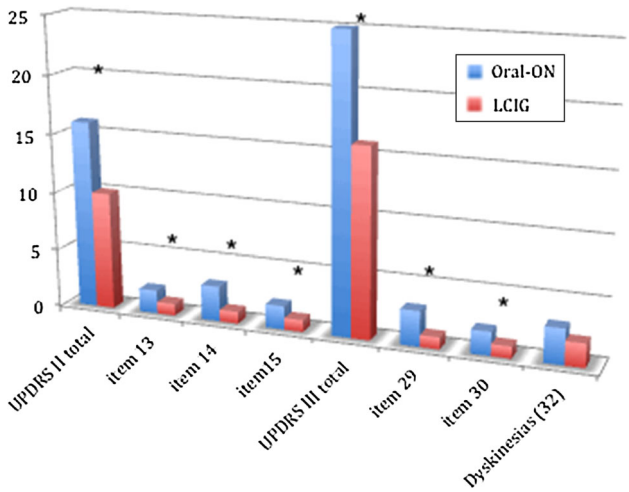

Fig. 1 UPDRS scores under O-LD and LCIG treatment

FOG. On the other hand, further increase of O-LD schedule, needed to relieve gait disorders, was prevented by dyskinesias worsening. In these patients, compared with O-LD, LCIG allowed higher and more stable peripheral LD levels, obtaining greater clinical efficacy and avoiding plasmatic LD peaks and troughs which are associated with dyskinesias or poor tolerability. Indeed, many studies demonstrated a sustained improvement in UPDRS III scores on LCIG compared with oral therapy along with a reduction of dyskinesia scores [9, 10].

By contrast, 3 patients of our cohort (Subgroup 2; see pt 7 in video sections 3–4) also achieved a clear improvement of gait after starting LCIG therapy but, interestingly, the total LD dose on LCIG was lower compared with the pre-infusional O-LD. In these patients, "On-FOG" was possibly due to overstimulation by peak-dose O-LD therapy. This phenomenon may be related to a dysfunction of the "higher-level" locomotor control system, including the basal ganglia and prefrontal cortex circuits, modulated by sensory feedback via afferent pathways (somesthetic, vestibular and visual systems). Dopaminergic overstimulation can lead to dysfunction of fronto-subcortical circuits which prompt "high-order" gait abnormalities, such as difficulties in appropriate foot placement when walking and problems with initiation/maintaining stepping.

"Freezing-on" represents a therapeutic challenge in clinical practice: reduction of O-LD may alleviate FOG, but often results in unacceptable worsening of others PD features and STN-DBS is not recommended considering the lack of benefit on LD refractory symptoms and the potential surgical risks [11]. By contrast, LCIG enables achievement of steady LD plasma concentration, within the individual therapeutic window, avoiding overstimulation of fronto-striatal pathways.

We acknowledge that our sample is small, the study retrospective, the UPDRS evaluation was not blinded to treatment condition and we had no pharmacokinetic data. Nonetheless, the observation that in PD patients with FOG not improved by adjustments of oral dopaminergic therapy continuous stimulation provided by LCIG is helpful in both "On" and "Pseudo-on" FOG has important clinical consequences as it may reduce the risk of falls [12].

Conflict of interest Dr. Antonini and Ricchi received fees for speaker-related activities from AbbVie. No specific funding supported this research.

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