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Effects of intestinal Levodopa infusion on freezing of gait in Parkinson disease

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ABSTRACT

Objective: To determine the impact of levodopa-carbidopa intestinal gel (LCIG) infusion on different subtypes of freezing of gait (FoG) classified according to levodopa responsiveness in advanced Parkinson disease (PD) patients.

Methods: We retrospectively assessed the presence and severity of FoG in 32 advanced PD patients based on the Unified PD Rating Scale (UPDRS) item 14 score. Different FoG subtypes were inferred from the score variation with oral dopaminergic medications. Modifications following long-term LCIG infusion were analysed. Motor symptoms and motor complications were assessed by UPDRS part III and IV respectively.

Results: FoG related UPDRS score varied from 2.6 ± 0.9 in OFF condition to 0.9 ± 0.8 in the ON condition at baseline and improved to 0.6 ± 0.7 with LCIG infusion ($p = 0.027$). After a mean of 2.59 ± 1.12 years of continuous LCIG infusion, Pseudo-ON-FoG improved to a greater extent with LCIG infusion than with oral therapy in 12 patients (38%) and equally well in 8 patients (25%), OFF-type-FoG was controlled equally well in 8 patients (25%) and worsened slightly in 3 patients (9%). Unresponsive-FoG, present in one patient (3%), was unmodified by LCIG infusion.

Conclusions: Even though limited by the subjective simple measure of FoG, this study suggests that patients undergoing LCIG infusion maintain a good long-term control of FoG. Pseudo-on-FoG improves in a considerable percentage of patients and OFF-type-FoG remains well controlled with LCIG infusion. Further studies with a larger number of patients and objective measures of FoG are needed to confirm these findings.

1. Introduction

Freezing of gait (FoG) is a common and disabling symptom in advanced Parkinson's disease (PD) [1]. The pathophysiology of FoG remains incompletely understood. Although both dopaminergic and non-dopaminergic mechanisms are involved, its treatment is a clinical challenge, especially in those cases refractory to oral therapy modifications [2].

Based on the spectrum of response to dopaminergic medications, 4 different types of FoG have been characterized; 1) The most common is OFF-type-FoG, which is relieved by dopaminergic medications, improving or disappearing in the ON state; it is a common manifestation of motor fluctuations associated with a low dopaminergic drive; 2) Pseudo-ON-FoG is present during a seemingly optimal ON state but improves with stronger dopaminergic stimulation; 3) Unresponsive-FoG is defined by the presence of FoG in both OFF and ON state, and it is not influenced by medication; 4) True-ON-FoG, is a relatively rare type of FoG which is absent during OFF periods and occurs exclusively in the ON state [3,4].

The constant dopaminergic drug delivery attained by LCIG infusion allows a significant reduction of motor fluctuations in patients with advanced PD [5] and its efficacy in the long-term management of motor complications has been confirmed by several case series [6,7]. The effect of LCIG treatment on different types of FoG has not been studied systematically so far. Recently, preliminary reports based on small samples, describe an improvement of FoG with LCIG of a greater magnitude than those obtained with oral medical therapies [8,9]. A prospective, open label study on five PD patients with disabling FoG documented that 24-h LCIG infusion reduces oral-levodopa unresponsive-FoG and associated falls [8]. Moreover, LCIG therapy was shown to be effective in seven PD patients with prominent episodes of freezing refractory to oral therapy [9].

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In order to better define the impact of LCIG on FoG we assessed the presence and severity of different FoG subtypes before and after LCIG treatment in 32 PD patients treated at our Centre between 2010 and 2014.

2. Methods

We collected data from 32 consecutive PD patients treated with LCIG infusion (Duodopa©, AbbVie, North Chicago, IL, USA) at the Department of Neuroscience, University of Turin. Each patient signed a written informed consent to participate in the study. The Ethical Committee of the Hospital approved the study protocol.

All patients fulfilled the UK-Brain-Bank criteria [10] for the diagnosis of idiopathic PD and presented motor fluctuations and dyskinesia despite receiving optimized oral medications. Atypical parkinsonian features or dementia associated with PD represented exclusion criteria. Patients received an implant of percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) between 2010 and 2014 following a previously described procedure [11].

The unified Parkinson disease rating scale (UPDRS), Schwab & England (S&E) scale for activities of daily living (ADL) and Hoehn & Yahr (H&Y) scale were assessed at two time-points, at baseline before starting LCIG treatment and at follow-up during LCIG infusion. At baseline the assessment was carried out in two conditions, the practically defined OFF condition (following an overnight withdrawal of antiparkinsonian medications) and the ON condition (after the administration of 1.5 X the usual levodopa morning dose); at follow-up the assessment was carried out in daily-ON condition (during LCIG infusion).

Freezing of gait (FoG) was evaluated by means of Item-14 of the UPDRS part-II with a score ranging from 0 to 4 (0 = none; 1 = rare freezing when walking, may have start hesitation; 2 = occasional freezing when walking; 3 = frequent freezing, occasionally falls from freezing; 4 = frequent falls from freezing); falling (unrelated to freezing) according to Item-13 (0 = none; 1 = rare falling; 2 = occasionally falls, less than once per day; 3 = falls an average of once daily; 4 = falls more than once daily) and gait according to item-29 (0 = normal; 1 = walks slowly, may shuffle with short steps, but no festination or propulsion. 2 = walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion. 3 = severe disturbance of gait, requiring assistance. 4 = cannot walk at all, even with assistance). At baseline evaluation during oral therapy, patients gave 2 answers, one related to medication OFF condition (i.e. in the absence of pharmacological benefit), and one related to medication ON condition (i.e. when patients experienced the best effect of pharmacological therapy). At follow-up evaluation with LCIG infusion, given the significant reduction in the proportion of the waking day spent in OFF condition, the assessment was representative of the stable medication ON condition.

FoG was further categorized in four different subtypes based on the score of UPDRS item-14 in medication ON and OFF conditions at baseline evaluation. OFF-type-FoG was defined if FoG was present exclusively in OFF condition and absent during ON condition (UPDRS item-14 OFF > 0 and ON = 0); Pseudo-ON-FoG was defined if FoG was present in OFF condition and improved but did not disappear completely in ON condition (UPDRS item-14 OFF > ON > 0); Unresponsive-FoG was defined when FoG was unchanged in both OFF and ON conditions (UPDRS item-14 OFF = ON > 0); True-ON-FoG was defined when FoG was present exclusively in ON condition and absent in OFF (UPDRS item-14 OFF = 0 and ON > 0) [3,4].

Pharmacological therapy for motor and non-motor features was noted for each patient at baseline and follow-up evaluation.

2.1. Statistical analysis

Continuous variables were noted as mean and standard deviation and discrete variables as median and interquartile range (IQR, 25th–75th percentile). The Wilcoxon rank sum test was applied for comparisons of continuous variables before and after LCIG infusion. The Fisher test was used to compare nominal data. The primary outcome measure was the change in UPDRS item-14 (FoG) before and after LCIG and the secondary outcome measures were changes in UPDRS motor score (part-III), ADL (UPDRS part-II), falls unrelated to freezing (UPDRS item-13), gait (UPDRS item 29), motor complications (UPDRS part-IV), H&Y stage, S&E scale for ADL and levodopa equivalent daily dose (LEDD). Preoperative characteristics of patients with and without FoG improvement were compared using Mann-Whitney or chi square tests for continuous or categorical values, respectively. All tests were 2-sided; $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS v22 for MAC.

3. Results

Patients were evaluated at baseline and after a mean of 2.59 ± 1.12 years (range 0.85–4.25y). During this period a progression of disease was evident. H&Y ON-medication score deteriorated from 2.4 ± 0.9 to 2.8 ± 0.9 ($p = 0.015$) and S&E scale ON-medication score worsened from 77.8 ± 15.2 to 66.3 ± 19.1 ($p < 0.001$). With LCIG infusion there was a 61% reduction of daily OFF period duration ($p < 0.001$) and a 25% reduction in dyskinesia duration ($p = 0.021$) (Table 1).

Continuous LCIG infusion was maintained for an average of 13.9 ± 1.6 h during daytime; LEDD remained substantially stable, with a slight decrease from 1454.5 ± 410.9 to 1371.2 ± 314.8 mg/day ($p = 0.383$). The proportion of patients using dopamine agonists dropped from 66% to 31% with LCIG ($p = 0.011$) and the proportion of patients taking catechol-*O*-methyl-transferase-inhibitors dropped from 39% to 3% with LCIG ($p = 0.001$). The proportion of patients taking monoamine-oxidase-inhibitors, amantadine and extended-release-levodopa at bedtime did not vary significantly. There was an increase in the proportion of patients taking quetiapine (from 16% to 44% at follow-up evaluation, $p = 0.024$) while the proportion of patients taking benzodiazepines and antidepressants did not vary significantly (Table 1).

FoG related UPDRS score varied from 2.6 ± 0.9 in OFF condition to 0.9 ± 0.8 in ON condition at baseline ($p < 0.001$) and improved further to 0.6 ± 0.7 with LCIG infusion ($p = 0.027$, compared to baseline ON condition; Fig. 1 and Table 1). Falls related UPDRS score varied from 2.5 ± 0.8 in OFF condition to 0.7 ± 1.0 in ON condition at baseline ($p < 0.001$) and to 0.6 ± 1.0 with LCIG infusion ($p = 0.726$, compared to baseline ON condition). Gait related UPDRS score varied from 2.6 ± 0.8 in OFF condition to 1.2 ± 0.9 in ON condition at baseline ($p < 0.001$) and to 1.4 ± 1.1 with LCIG infusion ($p = 0.331$, compared to baseline ON condition)(Table 1).

All 32 patients showed FoG at baseline, categorized as Pseudo-ON-FoG in 20 patients (63%), OFF-type-FoG in 11 patients (34%) and Unresponsive-FoG in 1 patient (3%) (Fig. 2). Pseudo-ON-type FoG improved to a greater extent with jejunal infusion than with oral therapy in 12 of 20 subjects, whereas it responded equally well in the remaining 8 subjects. The proportion of patients using dopamine agonists decreased from baseline (8 out of 12) to LCIG infusion (2 out of 12) ($p = 0.036$), although total LEDD did not vary significantly before and after LCIG infusion.

Patients showing FoG improvement with LCIG had a better UPDRS-I score at baseline ($p = 0.032$), a worse UPDRS-II score in OFF condition ($p = 0.040$) and a shorter disease duration ($p = 0.039$), compared to patients with FoG responding equally well to LCIG infusion.

OFF-type-FoG responded equally well to jejunal infusion in respect to oral therapy in 8 of 11 subjects whereas in 3 patients it worsened from a score of 0 (freezing absent) with oral therapy to a score of 1 (rare freezing while walking) during LCIG infusion. The proportion of these patients on dopamine agonists and total LEDD did not differ significantly before and during LCIG infusion. Patients showing a