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ORIGINAL COMMUNICATION

Long-term duodenal levodopa infusion in Parkinson's disease: a 3-year motor and cognitive follow-up study

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Abstract Duodenal infusion of levodopa/carbidopa gel (Duodopa) is an effective treatment option for advanced Parkinson's disease (PD). Long-term clinical experience up to 16 years suggests that the safety of this procedure is acceptable, while several observational studies showed that Duodopa reduces motor fluctuations and dyskinesias improving patients' quality of life (QoL). The aim of this study is to investigate the long-term motor and cognitive outcome of Duodopa treatment in advanced PD patients and its' impact on the QoL. Twenty-five consecutive PD patients were assessed using the Unified PD rating scale (UPDRS), a battery of neuropsychological tests, and the PD questionnaire (PDQ-39) at baseline and after a mean period of three years of Duodopa treatment. Seventeen out of 25 patients reached the follow-up evaluation; five patients discontinued Duodopa and three patients died of causes unrelated to drug infusion. Duodopa improved motor complications (UPDRS-IV) and quality of life (PDQ-39). A sub-group of subjects (41 %) developed a significant deterioration of cognitive functions over time. The most common adverse events were dislocation and the kinking of the intestinal tube. In conclusion, Duodopa therapy is effective in the long-term treatment of advanced PD patients. Continuous enteral levodopa infusion achieves a reduction of motor fluctuations and dyskinesias improving patients' QoL, despite the progression of PD motor symptoms and a significant decline in cognitive functions in a sub-group of patients.

Keywords Parkinson's disease · Levodopa/carbidopa duodenal infusion · Motor fluctuations · Dyskinesias

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Introduction

Intraduodenal delivery of levodopa/carbidopa gel (Duodopa) is an effective therapeutic option for the treatment of advanced Parkinson's disease (PD) complicated by motor fluctuations and dyskinesias [1]. The direct intestinal infusion of Duodopa has been shown to provide a more stable plasma levodopa concentration, allowing a better control of motor fluctuations and dyskinesias [2].

Randomized controlled clinical trials have shown that Duodopa infusion reduces "off" time and increases "on" time without dyskinesia [3–5]; further observational studies confirmed that Duodopa reduced motor fluctuations and improved the Unified PD rating scale (UPDRS) scores and quality of life (QoL) measures, after six months to two years of continuous infusion [6–11]. A prospective observational study, focused on non-motor symptoms, also showed a significant improvement of sleep disorders, fatigue, cognition, cardiovascular, gastrointestinal and urinary symptoms in 22 advanced PD patients over a period of six months [12].

Moreover, a clinical profile of PD patients receiving this therapy, along with data on effectiveness and safety, has been described in a questionnaire-based retrospective review of data for 91 patients treated with Duodopa in France between 2003 and 2007 [13]. Severe motor

complications were the main indication for Duodopa infusion and, in the vast majority of these patients, Duodopa represented the last line of therapy because other therapeutic options such as apomorphine pump or deep brain stimulation had failed or were contraindicated [13]. Concerning the safety and feasibility of long-term treatment, Nyholm and colleagues [14], in the retrospective review of their long-term clinical experience with continuous infusion up to 10 years, found that the adverse event profile of Duodopa was similar to that of oral levodopa, even though several technical problems with the infusion system occurred in the majority of patients. Nevertheless, for most patients the technical challenges posed by the intestinal infusion system were offset by the improvement of motor fluctuations and dyskinesias. The same group recently published the retrospective review of medical records of 135 patients treated with Duodopa up to 16 years, finding that device-related problems were the most common reason for infusion discontinuation [15].

However, follow-up studies of Duodopa treatment are relatively heterogeneous. In fact, some reports consider UPDRS and PDQ-39 measures of QoL [6–8, 11] while some studies relay on patient's diaries and on clinical global impression of change [8, 13]; some other study instead focus exclusively on non-motor aspects [12] or QoL measures [10]. In addition, selection criteria for enrolment are quite different mainly concerning cognitive impairment. Dementia is present in 50 % of PD patient enrolled in the French multicentre study [13], while other studies either included only patients without dementia [6–9, 13] or did not mention the cognitive status of patients [14, 15].

In order to evaluate the long-term effectiveness of Duodopa and its impact on the health related QoL, in this study we prospectively investigated the motor and cognitive outcome of a group of advanced PD patients undergoing continuous Duodopa infusion over a mean period of three years.

Materials and methods

Patients

We assessed 25 consecutive PD patients, 16 males and nine females, with a mean age of 69.9 ± 5.8 years, a mean age at PD onset of 57.8 ± 7.3 years and a mean disease duration of 12.1 ± 4.1 years, who started Duodopa infusion at our centre between 2005 and 2009. The diagnosis of idiopathic PD was made according to the UK Brain Bank criteria [16] and all patients showed motor fluctuations and dyskinesias refractory to conventional oral therapy since a mean period of 5.2 ± 3.1 years. The presence of a response to levodopa with a reduction >33 % of Unified PD Rating Scale (UPDRS) motor score was a prerequisite. We did not include patients with atypical parkinsonian features or patients with dementia, diagnosed according to criteria for dementia associated with PD [17]. All patients included in the study signed a written informed consent.

Duodopa procedure

Patients were switched from their conventional oral therapy to Duodopa, a water suspension of micronized active compound levodopa (20 mg/mL) and carbidopa (5 mg/mL) in 2.95 % carboxymethylcellulose gel (Abbott Products, GmbH, Hannover, Germany) [18]. Duodopa initiation required hospitalisation for an average period of 11 days (range 7–17 days). Duodopa was first administered during three consecutive days for a mean of 14 h/day through a temporary nasoduodenal tube connected to a portable pump (CADD-Legacy Duodopa; Smiths Medical, Minneapolis, MN). The initial maintenance dose was calculated according to the levodopa equivalent daily dose (LEDD) [19]; the optimal dose was then titrated individually by steps of 2–4 mg of levodopa per hour (0.1–0.2 mL/h), until reaching the maximal motor performance without relevant dyskinesias. Duodopa effectiveness was assessed for three days through the treatment response scale [5], before performing a percutaneous endoscopic gastrostomy (PEG) for the permanent positioning of the enteral connection device.

Over time, four different systems were used for the percutaneous enteral connection: the Entristar skin level gastrostomy system (Tyco Healthcare) in the first five patients, the Kimberly–Clark enteral tube (Mic-Key) in six patients, the Flocare Bengmark tube (Nutricia Healthcare, Switzerland) in four patients, and the Endovive two-port TTP jejunal feeding tube kit (Boston Scientific, Spencer, IN, USA) in the remaining 10 patients. Entristar, Flocare and Endovive have an internal retention bolster, whereas the Kimberly–Clark enteral tube retention system was based on a ballooned retained tube. The total daily dose of Duodopa was composed of a morning bolus dose, the continuous maintenance dose, and the extra bolus doses, ranging from 20 to 50 mg of levodopa (1.0–2.5 mL infusion) when needed.

Patients' evaluations

Patients were assessed at baseline before the initiation of Duodopa infusion and prospectively in a scheduled evaluation after a mean period of 36.2 ± 11.5 months of continuous infusion treatment. The first evaluation took place during the hospitalisation preceding the PEG procedure; parkinsonian motor features were assessed by means

of the UPDRS part III in the morning, after overnight withdrawal of antiparkinsonian medication ("off" condition) and following the administration of 1.5 × the usual levodopa morning dose ("on" condition). At follow-up evaluation, UPDRS part III was assessed in the morning before starting Duodopa ("off" condition) and 60–90 min after starting Duodopa infusion (daily "on" condition). The subscore for axial symptoms, including speech (item 18), arising from a chair (item 27), posture (item 28), gait (item 29), postural stability (item 30), was analysed separately. Activities of daily living (ADL) were evaluated by means of the UPDRS part II. Complications of therapy were assessed by means of the UPDRS part IV total score and subitems for dyskinesia duration (item 32) and "off" period duration (item 39).

Neuropsychological and behavioural assessments were performed in the best clinical condition ("on" condition) at baseline and at the follow-up visit. The mini-mental state examination (MMSE) was assessed as a screening measure of global cognitive functioning. A test battery [20] assessed five cognitive domains: reasoning [Raven Color Matrices test (CPM47)] [21], memory [Bisyllabic Words Repetition test (BWR), Corsi's Block Tapping test (CBT) and Rey auditory verbal learning (AVLT)] [22, 23], attention [Digit Cancellation Test (DCT), Trail Making A (TMA)] [22, 24], frontal executive functions [Trail Making B test (TMB), Frontal Assessment Battery (FAB) and Clock Drawing test (CDT)] [24–26], and phonemic and category verbal fluency [22, 27].

Mild cognitive impairment (MCI) was defined by a deficit of at least 1.5 standard deviations below the expected age corrected mean score either in one cognitive domain (single domain MCI) or in two or more cognitive domains (multiple domain MCI); individuals had subjective cognitive complaints, but cognitive deficits did not result in significant functional decline [28]. A clinical diagnosis of probable dementia (ProD) was made following diagnostic criteria for dementia associated with PD, proposed by Emre and colleagues [17], which require the presence of severe impairment in at least two cognitive domains and deficits severe enough to impair daily life independent of the impairment ascribable to motor symptoms.

Health related quality of life was assessed with the Parkinson's disease Questionnaire (PDQ-39) [29] compiled by the patients with the assistance of the caregiver.

Pharmacological therapy for parkinsonian motor and non-motor features was noted for each patient at baseline and at the follow-up evaluation. All adverse events occurring during Duodopa treatment were collected and classified according to their relationship with (1) Duodopa infusion, (2) gastrostomy, or (3) technical problems related to the infusion devices.

Statistical analysis

In addition to descriptive statistics, the nonparametric Wilcoxon-signed-rank test was used for group comparisons of variables at baseline and follow-up evaluations. The Fisher exact probability test was used to compare the proportions of patients taking different drugs before and after Duodopa infusion. All p values reported are two-tailed and a p value <0.05 was considered statistically significant. The analyses were performed using SPSS 19 for Mac.

Results

Of the 25 PD patients who initiated Duodopa between 2005 and 2009, 17 patients reached the scheduled follow-up evaluation after a mean time period of 36.2 ± 11.5 months (Fig. 1). Three patients died for causes that were considered unrelated to Duodopa treatment (pneumonia in two patients and sepsis in one patient) after a period of 4.9, 17.2 and 24.4 months of infusion. Five more patients discontinued Duodopa before the scheduled visit; the reasons of treatment discontinuation were repeated problems with the infusion device in three patients (combined with cognitive decline, confusion and abdominal pain respectively), gastrostomy dislocation in one patient and the diagnosis of a genetic polyneuropathy in another patient.

A comparison of the baseline characteristics of the eight patients who did not reach the 3-year observation with the 17 patients who completed the study did not reveal any significant difference for neither UPDRS part II, III and IV, PDQ-39 or any neuropsychological test score.

Motor symptoms, ADL, complications of therapy and QoL

The comparisons of UPDRS and PDQ-39 scores of the 17 PD patients at baseline and at follow-up assessment are shown in Table 1.

PD symptoms measured by the UPDRS part III motor score and the subscore for axial symptoms worsened significantly between baseline and follow-up assessment in both "off" and "on" conditions (UPDRS III total score varied from 43.1 ± 13.7 to 48.4 ± 12.4 in "off" condition, $p < 0.05$, and from 23.2 ± 9.2 to 32.2 ± 12.6 in "on" condition, $p < 0.01$. Axial score varied from 11.1 ± 4.6 to 13.5 ± 4.7 in "off" condition, $p < 0.01$, and from 5.8 ± 3.5 to 10.2 ± 4.3 in "on" condition, $p < 0.01$).

The ADL score worsened significantly only in the "on" condition while in the "off" condition it did not show significant differences between baseline and follow-up evaluation (UPDRS part II score varied from a value of

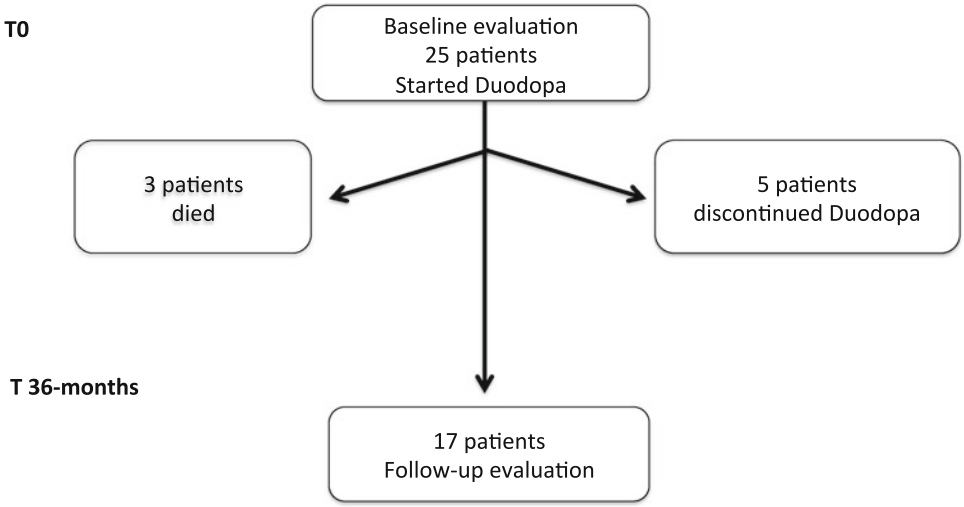

Fig. 1 Flow chart of the study

Table 1 UPDRS and PDQ-39 scores of patients at baseline and after 3 years of continuous therapy with Duodopa

	17 PD patients		7 PD patients ProD		10 PD patients no-ProD	
	Baseline	3-year follow-up	Baseline	3-year follow-up	Baseline	3-year follow-up
UPDRS-III score (motor)						
Off med	43.1 (13.7)	48.4 (12.4)*	46.4 (12.5)	54.5 (9.1)*	40.9 (14.6)	44.2 (13.0)
On med	23.2 (9.2)	32.2 (12.6)**	25.4 (9.5)	41.1 (10.9)*	21.6 (9.1)	25.3 (9.1)
UPDRS-III axial score						
Off med	11.1 (4.6)	13.5 (4.7)**	12.0 (4.7)	16.4 (2.5)*	9.6 (4.0)	11.5 (4.5)
On med	5.8 (3.5)	10.2 (4.3)**	5.6 (3.0)	12.7 (3.3)*	5.4 (3.1)	8.2 (3.6)*
UPDRS-II score (ADL)						
Off med	23.2 (8.5)	25.3 (7.3)	24.6 (9.4)	29.9 (5.1)	22.2 (9.4)	22.1 (7.1)
On med	16.1 (7.2)	20.9 (7.5)*	17.1 (7.3)	23.5 (6.4)*	15.4 (7.5)	19.0 (8.0)
UPDRS-IV (complications of therapy)	8.4 (3.2)	5.6 (2.8)**	8.4 (2.6)	5.4 (2.3)*	8.5 (3.7)	5.0 (3.1)*
Dyskinesias duration (item 32)	1.9 (1.0)	1.1 (1.0)*	1.9 (0.4)	1.1 (1.2)*	1.9 (1.3)	1.1 (0.9)*
Off period duration (item 39)	1.6 (0.8)	0.8 (0.6)**	1.6 (0.7)	0.9 (0.5)*	1.5 (0.9)	0.7 (0.6)*
PDQ-39 Summary Index	59.2 (18.7)	43.1 (13.9)**	71.3 (16.5)	53.8 (13.0)*	50.7 (15.7)	35.6 (8.9)**
Mobility	64.9 (25.7)	50.2 (23.8)*	76.7 (22.5)	57.8 (26.7)*	56.7 (25.6)	44.8 (21.3)*
Activity of daily living	65.8 (16.7)	44.7 (20.0)*	77.6 (8.0)	48.5 (26.2)*	57.5 (16.3)	42.0 (15.4)*
Emotional well being	55.0 (26.2)	32.6 (19.8)*	56.7 (26.2)	38.9 (25.7)	47.4 (24.7)	28.1 (14.3)*
Stigma	50.0 (27.0)	31.0 (20.5)*	62.8 (23.5)	29.8 (19.5)*	41.1 (26.7)	31.8 (22.2)*
Social support	34.6 (26.9)	23.3 (32.7)*	40.8 (26.6)	27.7 (40.2)*	30.2 (27.6)	20.2 (28.1)
Cognition	40.8 (22.7)	31.7 (22.7)	48.5 (25.8)	40.5 (30.8)	35.4 (19.8)	25.5 (13.4)
Communication	49.3 (18.2)	37.2 (22.0)*	62.2 (9.6)	44.3 (23.5)	40.3 (17.6)	32.1 (20.5)
Bodily discomfort	45.5 (36.8)	30.4 (20.6)	64.6 (27.6)	28.8 (26.2)	32.1 (37.5)	31.4 (17.1)

The outcome measures are given for all PD patients who reached the follow-up evaluation ($n = 17$) and separated for PD patients who developed probable dementia (ProD, $n = 7$) and patients without significant cognitive decline (no-ProD, $n = 10$). Values are given as mean (SD)

* $p < 0.05$; ** $p < 0.01$; Wilcoxon test compared to baseline values

23.2 ± 8.5 to 25.3 ± 7.3 in "off" condition, p = n.s., and from 16.1 ± 7.2 to 20.9 ± 7.5 in "on" condition, $p < 0.05$).

There was a 33 % improvement of the complications of therapy (UPDRS part IV total score varied from 8.4 ± 3.2 at baseline to 5.6 ± 2.8 at follow-up, $p < 0.01$), including

a 42 % improvement of the item for dyskinesia duration (item 32, from a score of 1.9 ± 1.0 to 1.1 ± 1.0, $p < 0.05$) and a 50 % improvement of the item for "off" period duration (item 39, from a score of 1.6 ± 0.8 to 0.8 ± 0.6, $p < 0.05$).

Quality of life improved significantly after 3 years of Duodopa treatment, with a 27 % reduction of the PDQ-39 summary index (from a value of 59.2 ± 18.7 at baseline to 43.1 ± 13.9 at the follow-up visit, $p < 0.05$).

Neuropsychological evaluation

At baseline evaluation, 4 out of 17 patients (23 %) had a normal neuropsychological profile, 6 patients (35 %) had single domain MCI, and 7 patients (41 %) had multiple domain MCI. At follow-up evaluation after a mean period of 3 years, two patients (12 %) had normal neuropsychological profiles, two patients (12 %) single domain MCI, six patients (35 %) had multiple domain MCI and seven patients (41 %) progressively developed a cognitive decline meeting criteria for the diagnosis of ProD.

Analysing the modification of test scores for the group of seven patients who developed ProD, a marked deterioration in all cognitive domains was found (Table 2). MMSE significantly worsened from a mean value of 24.7 ± 2.7 at baseline to 15.6 ± 3.7 at follow-up evaluation, ($p < 0.01$). A significant decline was detected in memory functions, especially in short-term visual-spatial memory (CBT score varied from 3.4 ± 1.1 to 1.1 ± 1.2, $p < 0.01$) and in verbal long-term learning (AVLT score varied from 22.6 ± 8.3 to 7.6 ± 8.6, $p < 0.01$). Concerning attention, all test scores worsened, in particular there was a significant decline in selective attention (evaluated by DCT—from 26.0 ± 10.0 to 8.4 ± 0.6, $p < 0.01$) and in visual-motor speed and sustained attention (TMA score varied from 261.6 ± 119.2 at baseline to 509.0 ± 156.1 at follow-up, $p < 0.01$). There was a marked and significant decline also in executive functions (TMB score varied from a mean baseline value of 415.3 ± 121.4 to 600.0 ± 0.0, $p < 0.05$; FAB score varied from 9.3 ± 2.1 to 4.3 ± 1.4, $p < 0.05$; CDT score varied from 2.6 ± 0.8 to 0.9 ± 1.5, $p < 0.01$) and in tasks measuring semantic and categorical lexicon recovery (Phonemic Verbal Fluency score ranged from 22.6 ± 8.8 to 5.0 ± 5.2, $p < 0.05$; Semantic Verbal Fluency score varied from 14.4 ± 6.4 to 6.0 ± 2.6, $p < 0.05$).

A decline in cognitive functions was also detected in the remaining group of 10 PD patients (MMSE score declined from 27.3 ± 0.9 to 24.4 ± 2.0, $p < 0.05$), although deterioration was confined to executive functions (FAB score declined from 12.6 ± 3.6 to 8.9 ± 2.4, $p < 0.05$; CDT score from 2.8 ± 0.9 to 1.3 ± 0.8, $p < 0.05$) and sustained attention (TMA score varied from 103.9 ± 59.5 at baseline to 142.8 ± 42.9 at follow-up, $p < 0.01$; and DCT score varied from 35.3 ± 8.8 at baseline to 28.8 ± 7.8 at follow-up; $p < 0.05$), whereas modifications in cognitive domains of reasoning, memory and language were not significant.

Scores obtained on the Apathy and Depression scales were just above the threshold of pathological range at baseline evaluation and did not vary significantly at the follow-up assessment for both patients with and without significant cognitive decline (BDI score ranged from 20.0 ± 5.7 at baseline to 17.1 ± 6.4 at follow-up, p = n.s., for patients with ProD and from 16.0 ± 10.3 to 17.3 ± 9.4, p = n.s., for patients without significant cognitive decline; Marin Apathy Scale, normal range 0–14; from 20.1 ± 8.3 to 18.4 ± 4.5, p = n.s. for patients with probable dementia and from 17.8 ± 7.2 to 19.2 ± 3.4, p = n.s., for patients without significant cognitive decline).

Sub-group analysis of outcome measures in patients with and without significant cognitive decline

Patients who developed ProD at follow-up evaluation ($n = 7$) and patients without significant cognitive decline (no-ProD) ($n = 10$) did not differ significantly for either age (67.7 ± 6.9 vs. 69.0 ± 6.1 years; p = n.s.), age at PD onset (54.9 ± 8.6 vs. 55.8 ± 7.2 years; p = n.s.), disease duration (12.9 ± 5.8 vs. 13.2 ± 3.1 years; p = n.s.), duration of motor complication (4.7 ± 1.7 vs. 6.5 ± 2.2 years; p = n.s.) and LEDD (975 ± 212 vs. 1,054 ± 310 mg/die; p = n.s.). In the ProD group, at baseline six patients (86 %) had a profile of multiple domain MCI and one patient (14 %) had a profile of single domain MCI. In the no-ProD group, at baseline four patients (40 %) had normal neuropsychological profiles, five patients (50 %) had single domain MCI and 1 patient had multiple domain MCI (10 %) while at follow-up assessment two patients (20 %) had normal neuropsychological profiles, two patients (20 %) had single domain MCI and 6 patients (60 %) had multiple domain MCI.

Between baseline and follow-up assessment, only patients with ProD showed a significant worsening of PD symptoms measured by the UPDRS part III total motor score and the sub-score for axial symptoms, in both "off" and "on" conditions (UPDRS III total score varied from 46.4 ± 12.5 to 54.5 ± 9.1 in "off" condition, $p < 0.05$, and from 25.4 ± 9.5 to 41.1 ± 10.9 in "on" condition, $p < 0.05$. Axial score varied from 12.0 ± 4.7 to 16.4 ± 2.5 in "off" condition, $p < 0.05$, and from 5.6 ± 3.0 to 12.7 ± 3.3 in "on" condition, $p < 0.05$) (Table 1; Fig. 2). No-ProD patients showed a significant worsening exclusively for axial symptoms in "on" condition (the axial score varied from a value of 5.4 ± 3.1 at baseline to 8.2 ± 3.6 at the follow-up visit, $p < 0.05$).

Table 2 Neuropsychological and behavioural assessments of PD patients at baseline and after 3 years of therapy with Duodopa

	7 PD patients ProD		10 PD patients no-ProD	
	Baseline	3 years follow-up	Baseline	3 years follow-up
MMSE	24.7 (2.7) [2]	15.6 (3.7)* [6]	27.3 (0.9) [0]	24.4 (2.0)* [2]
Reasoning				
Raven Matrices (PM47)	20.3 (8.2) [2]	3.0 (0.0)* [6]	20.7 (5.1) [2]	16.1 (8.1) [5]
Memory				
Words Rep. test (BWT)	4.4 (0.8) [0]	3.9 (1.1) [3]	5.0 (0.8) [0]	4.5 (1.2) [2]
Corsi's Tapping test (CBT)	3.4 (1.1) [3]	1.1 (1.2)* [7]	4.0 (1.1) [2]	3.4 (0.5) [6]
Rey AVLT	22.6 (8.3) [4]	7.6 (8.6)* [7]	29.6 (11.1) [3]	26.8 (7.9) [8]
Rey differed-AVLT (AVLT d)	3.1 (1.9) [4]	1.0 (1.8)* [6]	6.5 (3.1) [2]	4.9 (3.3) [4]
Attention				
Digit Cancellation test (DCT)	26.0 (10.0) [3]	8.4 (0.6)* [7]	35.3 (8.8) [2]	28.8 (7.8)* [6]
Trail Making A (TMA)	261.6 (119.2) [6]	509.0 (156.1)* [7]	103.9 (59.5) [4]	142.8 (42.9)* [6]
Executive functions				
Trail Making B (TMB)	415.3 (121.4) [6]	600.0 (0.0)* [6]	385.0 (207.1) [3]	424.9 (188.8) [7]
Frontal Ass Battery (FAB)	9.3 (2.1) [6]	4.3 (1.4)* [7]	12.6 (3.6) [3]	8.9 (2.4)* [8]
Clock Drawing test (CDT)	2.6 (0.8) [3]	0.9 (1.5)* [5]	2.8 (0.9) [2]	1.3 (0.8)* [5]
Language				
Phonemic verbal fluency	22.6 (8.8) [2]	5.0 (5.2)* [6]	26.5 (5.6) [0]	20.0 (7.0) [4]
Category verbal fluency	14.4 (6.4) [0]	6.0 (2.6)* [5]	13.8 (3.1) [0]	12.1 (3.5) [1]
Mood				
Beck Depression Inventory (BDI)	20.0 (5.7)	17.1 (6.4)	16.0 (10.3)	17.3 (9.4)
Apathy				
Marin Apathy Scale	20.1 (8.3)	18.4 (4.5)	17.8 (7.2)	19.2 (3.4)

Mean values (SD) of test scores and number of patients with test scores below cut-off values (in square brackets) for PD patients who developed probable dementia (ProD, $n = 7$) and PD patients without significant cognitive decline (no-ProD, $n = 10$)

* $p < 0.05$; ** $p < 0.001$; Wilcoxon test compared to baseline values

Likewise, the ADL score referred to the "on" condition worsened significantly only in ProD patients (the UPDRS II score varied from a value of 17.1 ± 7.3 at baseline to 23.5 ± 6.4 at the follow-up visit, $p < 0.05$).

Complications of therapy, including dyskinesia duration and "off" period duration improved significantly in both groups (UPDRS part IV total score varied from 8.4 ± 2.6 at baseline to 5.4 ± 2.3 at follow-up, $p < 0.05$, for ProD patients and from 8.5 ± 3.7 to 5.0 ± 3.1, $p < 0.05$, for no-ProD patients; item 32 score varied and from 1.9 ± 0.4 to 1.1 ± 1.2, $p < 0.05$, for ProD patients and from 1.9 ± 1.3 to 1.1 ± 0.9, $p < 0.05$, for no-ProD patients; item 39 score varied from 1.6 ± 0.7 to 0.9 ± 0.5, $p < 0.05$, for ProD patients and from 1.5 ± 0.9 to 0.7 ± 0.6, $p < 0.05$, for no-ProD patients).

Finally, Qol improvement measured by the PDQ-39 summary index was significant in both groups, even though the percentage improvement was slightly lesser in ProD patients (24 %) in respect to no-ProD patients (30 %) (PDQ-39 summary index varied from 71.3 ± 16.5 to 53.8 ± 13.0, $p < 0.05$, for ProD patients and from 50.7 ± 15.7 at baseline to 35.6 ± 8.9 at follow-up visit, $p < 0.05$, for no-ProD patients).

Pharmacological therapy

Table 3 summarises pharmacological therapy at baseline and at the follow-up evaluation with Duodopa infusion. Continuous infusion of Duodopa was performed for an average of 12.9 ± 1.8 h during the daytime; the mean levodopa dose at follow-up evaluation in the 17 patients was $1{,}127 \pm 279$ mg/day (range 700–1,556 mg), slightly increased from the baseline pre-treatment LEDD of $1{,}021 \pm 269$ mg/day (range 640–1,650 mg; Wilcoxon test, $p < 0.05$). Duodopa was used as mono-therapy during the daytime in all but two patients for whom pramipexole (2.1 mg/day) and rasagiline (1 mg/day) were maintained. Fourteen patients (82 %) used 1–2 extra doses of Duodopa per day with a mean dose of 1.8 ± 0.9 mL (36 mg).

The proportion of patients using dopamine agonists dropped from 48 % at baseline to 4 % with Duodopa (Fisher exact test, $p < 0.01$) and the proportion of patients

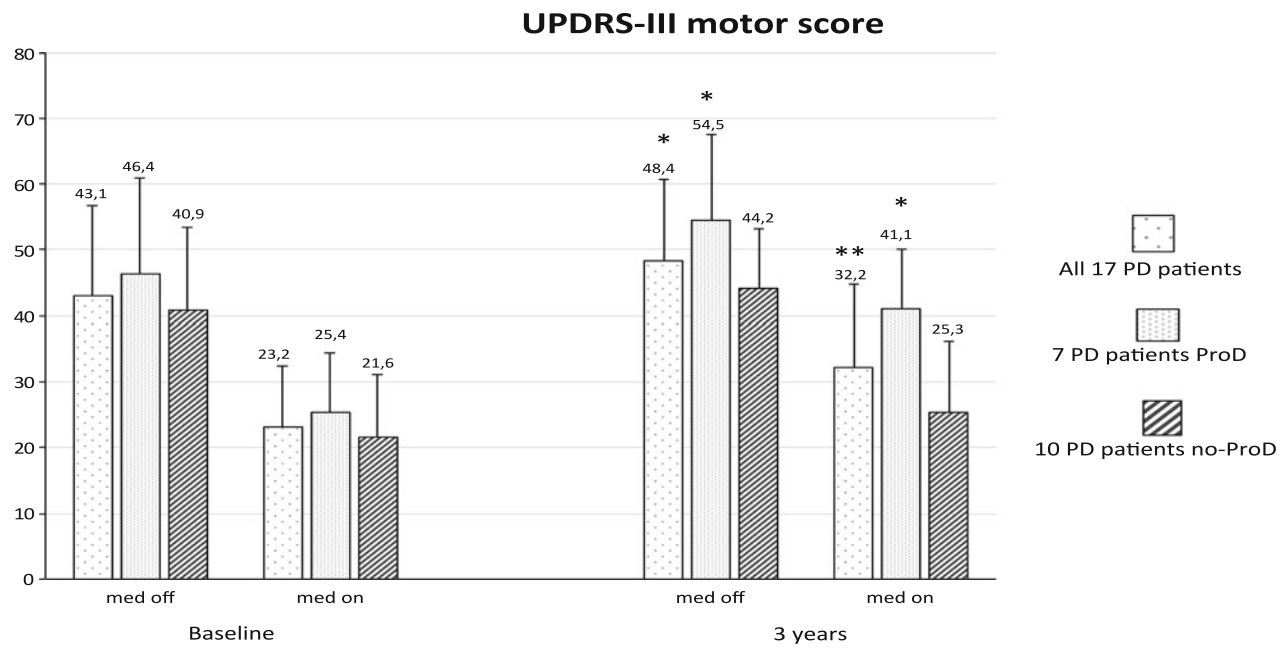

Fig. 2 UPDRS-III values of PD patients at baseline and at follow-up after 3 years of Duodopa infusion. The outcome measures are separated for PD patients who develop probable dementia (ProD, $n = 7$) and patients without significant cognitive decline (no-ProD, $n = 10$) at follow-up evaluation. *$p < 0.05$, **$p < 0.01$; Wilcoxon rank sum test compared to baseline values

Table 3 Pharmacological therapy of 25 PD patients

	Pharmacological therapy at baseline	Pharmacological therapy with Duodopa
LEDD (mg/day)	1,021 (269)	1,127 (279)*
Extended release levodopa at night	18 (75 %)	12 (48 %)
Dopamine agonists	12 (48 %)	1 (4 %)**
Pramipexole	8 (32 %)	1 (4 %)
Ropinirole	3 (12 %)	0 (0 %)
Pergolide	1 (4 %)	0 (0 %)
MAO-B inhibitor Rasagiline	3 (12 %)	2 (8 %)
COMT inhibitors	10 (40 %)	0 (0 %)**
Entacapone	9 (36 %)	0 (0 %)**
Tolcapone	1 (4 %)	0 (0 %)
Amantadine	5 (20 %)	5 (20 %)
Neuroleptics	7 (28 %)	15 (60 %)*
Clozapine	3 (12 %)	3 (12 %)
Quetiapine	4 (16 %)	12 (48 %)*
Antidepressants	6 (24 %)	5 (20 %)
Anxyolitics	8 (32 %)	6 (24 %)
Hypnotics	8 (32 %)	11 (44 %)

* $p < 0.05$; ** $p < 0.01$; Fisher exact probability test

taking catechol-O-methyl transferase inhibitors dropped from 40 % at baseline to 0 % with Duodopa ($p < 0.01$). The proportion of patients taking extended release levodopa at bedtime did not vary significantly (from 75 % at baseline to 48 % with Duodopa infusion, $p =$ n.s.).

There was an increase in the proportion of patients taking neuroleptics (from 28 % at baseline to 60 % at follow-up evaluation, $p < 0.05$) while the proportion of patients taking anxiolytics (32 vs. 24 %, $p =$ n.s.), hypnotics (32 vs. 44 %, $p =$ n.s.) and antidepressants (24 vs. 20 %, $p =$ n.s.) did not vary significantly.

Adverse events

Adverse events related to Duodopa infusion, surgery or the infusion devices are tabulated in Table 4 for all 25 patients. Adverse events related to the infusion devices were the most common complications, in particular the dislocation of the intestinal tube ($n = 34$) with retrograde migration from the small intestine to the stomach and the kinking or obstruction of the intestinal tube ($n = 24$). Device problems were a contributing reason for the discontinuation of infusion in 4 out of 5 patients.

Table 4 Adverse events in 25 PD patients during Duodopa infusion

Adverse events	No.
Related to Duodopa infusion	
Severe psychosis	1
Total	1
Related to gastrostomy	
Duodenal perforation	1
Phlegmon	1
Localized peritonitis	1
Intestinal volvulus	2
Peristomal infections	12
Total	17
Related to infusion devices (requiring replacement)	
Intestinal tube dislocated with migration in the stomach	34
PEG internal retention failure	12
Intestinal tube kinking or obstruction	24
PEG pulled out accidently	6
Total	85

In relation to Duodopa infusion, there was one case of psychosis that required Duodopa dose reduction and neuroleptic therapy. In relation to gastrostomy, there were several cases of peristomal infections ($n = 12$), all resolved with conservative medical therapy and one case of duodenal perforation that required surgical intervention and the subsequent positioning of a direct jejunostomy, two cases of intestinal volvulus resolved with the removal and repositioning of the intestinal tube, one phlegmon and one postoperative localized peritonitis.

Discussion

Our findings showed that continuous Duodopa infusion up to a mean period of three years effectively improves motor complications in advanced PD patients, with a significant decrease of the time spent in "off" condition and in "on" with dyskinesias. The measures of QoL by the PDQ-39 scale also showed an improvement in respect to the baseline condition, indicating an overall beneficial effect of Duodopa treatment. In our series of patients a considerable percentage (41 %) of subjects developed a significant deterioration of cognitive functions over time; therefore, we also analysed separately the two groups of patients. Patients who developed ProD showed a significant worsening of parkinsonian motor symptoms, in particular axial symptoms, both in "off" and "on" conditions, as well as a deterioration of ADL in "on" condition. On the other hand, patients without significant cognitive decline did not present significant deterioration of parkinsonian motor symptoms except for axial symptoms in "on" condition. Improvement of motor complications was significant in both groups, and so was the improvement of the PDQ-39 summery index score, albeit the percentage improvement was slightly better in no-ProD patients.

The improvement of motor fluctuations and dyskinesias over the mean period of 36 months is consistent with previous studies with shorter follow-up periods [3, 5, 6, 9]. Most of the studies documented no significant change of the UPDRS-III score in the "on" and "off" conditions comparing baseline to follow-up evaluations [3, 5, 6] and this is the case also for the sub-group of no-ProD patients in our study. By contrast, parkinsonian symptoms, and particularly axial symptoms deteriorated significantly over the 3-year period in ProD patients. In fact, a more rapid cognitive decline has been associated with the severity of motor symptoms [30] and motor subtype [31]. In particular, motor symptoms such as gait, speech, and postural disorders, are associated with accelerated decline in cognition [32]. Another study examining the rates of cognitive and motor decline over 2 years in PD and PD with dementia (PDD) found that mean UPDRS-III scores deteriorated in both patient groups, with a more rapid decline in the PDD group and that postural instability and gait difficulty (PIGD) motor subtype is associated with a faster rate of cognitive decline [33].

On the other hand, when considering the behavioural outcome, even though the scores on apathy and depression scales were just above the threshold of the pathological range, there were no significant changes in the scores during the course of follow-up. Interestingly, we found an improvement of PDQ-39 Summary Index score at follow-up evaluation both in ProD and no-ProD PD patients.

Overall the daily dose of levodopa increased only marginally (9 %) and pharmacological therapy was greatly simplified. At follow-up evaluation most patients used Duodopa as mono-therapy and therapy for behavioural symptoms was substantially unchanged with the exception of neuroleptics that were given to the majority of patients, possibly reflecting the progressive cognitive impairment.

A relatively high number of technical problems with the infusion device occurred during the follow-up. In this series of patients, the substitution of the infusion tube was not scheduled but was performed when a technical failure occurred. More recently, following the experience of our multidisciplinary team the tube replacement is usually scheduled every 12 months.

During the study period, five patients (20 %) discontinued Duodopa infusion and repeated device problems were a contributing cause in most cases. The rate and causes of discontinuation in our study where similar to those described in the retrospective review by Nyholm and colleagues [14, 15].

In conclusion, in this 3-year prospective assessment of a group of advanced PD patients undergoing continuous Duodopa infusion, we found a persistent reduction of motor fluctuations and dyskinesias with a consequent improvement of health related QoL, despite a worsening of PD motor symptoms and a significant decline in cognitive functions in a sub-group of patients. Moreover, even though enteral infusion of Duodopa was burdened by several device related complications, the beneficial effects of the treatment were maintained throughout the 3-year follow-up period.

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard The study has been approved by the San Giovanni Battista Molinette Hospital ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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