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Levodopa/carbidopa intestinal gel infusion in advanced Parkinson's disease: a 7-year experience

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Abstract

Background and purpose: Levodopa/carbidopa intestinal gel (LCIG) infusion is nowadays becoming an established therapeutic option for advanced Parkinson's disease (PD) patients with fluctuating symptoms unresponsive to conventional oral treatment. As the implementation of LCIG therapy is increasing, there is a need for safety and efficacy data from current clinical practice.

Methods: All PD patients treated with LCIG at our centre over a 7-year period were analysed to determine the duration of treatment, retention rate, reasons for discontinuation, LCIG efficacy in motor complications, modifications of concomitant therapy and adverse events.

Results: Of the 59 patients, seven subjects (12%) died of causes unrelated to LCIG infusion and 11 patients (19%) discontinued therapy prior to the cut-off date. Duodopa improved motor complications and over 90% of patients reported an improvement in their quality of life, autonomy and clinical global status. The most common adverse events were dislocation and kinking of the intestinal tube.

Conclusions: LCIG infusion is effective for the long-term treatment of advanced PD patients and exerts a positive and clinically significant effect on motor complications with a relatively low dropout rate.

Introduction

The cardinal symptoms of Parkinson's disease (PD), rest tremor, bradykinesia and rigidity, are effectively treated with a combination of oral levodopa and dopamine agonists during the early phase of the disease [1]. However, over time, in patients receiving long-term oral levodopa treatment the duration of the

response becomes shorter and motor fluctuations and dyskinesia develop [2]. Motor and non-motor symptom fluctuations reflect fluctuations in levodopa plasma concentrations resulting from the short half-life of levodopa and erratic absorption in relation to delayed gastric emptying [3]. Hence, the continuous drug delivery provided by intraduodenal administration of levodopa/carbidopa intestinal gel (LCIG) has been shown to achieve a more stable plasma concentration of levodopa in patients with advanced PD [4]. Indeed, nowadays LCIG, together with subcutaneous apomorphine infusion and deep brain stimulation, represents one of the available therapeutic options for patients with fluctuating symptoms unresponsive to conventional oral treatment [5].

Early randomized controlled clinical trials have shown that LCIG infusion effectively reduces daily 'off' time and motor fluctuations in advanced PD [6]. More recently, the large majority of studies analysed in a systematic overview of current research reported that LCIG is clinically effective in relieving symptoms of advanced PD and improving quality of life (QoL) compared with conventional oral therapy [7].

In the absence of well-controlled trials with a large number of patients, there is a need for safety and efficacy data from the implementation of LCIG therapy in clinical practice. An analysis was therefore conducted of all PD patients treated with LCIG at our centre over a 7-year period to determine the duration of long-term LCIG treatment, the retention rate and the reasons for LCIG discontinuation; further objectives included the assessment of LCIG efficacy on motor complications, QoL, autonomy and clinical global improvement, adverse events, dose modifications over time and changes of pharmacological therapy for motor and non-motor symptoms.

Patients and methods

Fifty-nine consecutive patients who started receiving long-term treatment with LCIG (Duodopa®; Abbott Products GmbH, Hannover, Germany) at our centre between May 2005 and December 2012 were included. Each patient signed an informed consent to participate in the study prior to undergoing percutaneous endoscopic gastrostomy (PEG). Torino University Hospital Ethical Committee approved the study protocol.

Patients fulfilled the UK Brain Bank criteria [8] for the diagnosis of idiopathic PD and presented motor fluctuations and dyskinesias despite receiving optimized oral medications. Patients with atypical parkinsonian features [9] or with dementia associated with PD [10] were not included.

Patients were switched from oral therapy to Duodopa, a water suspension of levodopa (20 mg/ml) and carbidopa (5 mg/ml) in 2.95% carboxymethylcellulose gel. Duodopa was first administered through a temporary naso-duodenal tube connected to the portable pump (CADD-Legacy® PCA-pump; Smiths Medical, St Paul, MN, USA). The initial maintenance dose was calculated according to the levodopa equivalent daily dose (LEDD) [11]; the optimal dose was titrated individually until reaching the maximal motor performance without relevant dyskinesia. LCIG effectiveness was assessed for 3–4 days and subsequently a PEG with the inner tube placed in the jejunum (PEG-J) was performed.

Four different systems were used, over the years, for the percutaneous enteral connection: the Entristar gastrostomy system (Tyco-Healthcare, Manchester, UK) in the first five patients, the Kimberly-Clark enteral tube (Kimberly-Clark, Irving, TX, USA) in six patients, the Flocare Bengmark tube (Nutricia-Healthcare Trowbridge, Wiltshire, UK) in nine patients and the Endovive TTP jejunal feeding tube (Boston Scientific, Spencer, IN, USA) in 39 patients.

The assessment of parkinsonian motor features took place just prior to the PEG procedure; the Unified PD Rating Scale (UPDRS) Part III was evaluated both in the 'off' condition, following an overnight withdrawal of antiparkinsonian medications, and in the 'on' condition, after the administration of 1.5× the usual levodopa morning dose. Activities of daily living were evaluated with UPDRS Part II and complications of therapy with UPDRS Part IV.

During a semi-structured interview with the patient and the caregiver, the neurologist assessed efficacy for motor complications (UPDRS Part IV), gait disorders, dysphagia, dysarthria (rated on a three-point scale: improvement, no change, worsening), QoL, autonomy and clinical global improvement (rated on a five-point scale: great improvement, moderate improvement, slight improvement, no change, worsening) [12].

All adverse events occurring during LCIG treatment were collected and categorized according to their relationship with (i) technical problems related to the infusion devices, (ii) gastrostomy or (iii) LCIG infusion [12].

Daily use of LCIG was investigated, including the total daily dose of infusion, the time of day at which infusion was started and stopped, and the involvement of a caregiver for setting up and shutting down the device. Pharmacological therapy for parkinsonian motor and non-motor features was noted for each patient at the baseline before starting long-term LCIG and at the follow-up evaluation.

Statistics

The non-parametric Wilcoxon signed-rank test was used for group comparisons of continuous variables. McNemar's test for dependent proportions was used to analyse changes of concomitant medications over time. All P values reported are two-tailed and a P value <0.05 was considered statistically significant.

Results

Over a 7-year period a total of 59 PD patients (40 males and 19 females) started long-term LCIG infusion; 25 of them had taken part in a previous prospective outcome study [13]. Demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of 59 patients treated with LCIG

		Mean	SD	Median	Range
Number of patients	59				
Sex (M/F; %)	40/19 (82%/18%)				
Age at LCIG initiation (years)		69.3	(5.9)	70	(56–80)
Age at PD diagnosis (years)		56.3	(7.1)	56	(37–67)
PD duration at LCIG initiation (years)		13.0	(3.8)	13	(7–24)
LCIG infusion duration at follow-up (months)		25.8	(19.5)	19	(3–87)
UPDRS III (Motor examination)	Off	46.5	(11.8)	46	(14–70)
	On	25.0	(10.3)	24	(6–42)
UPDRS II (Activities of daily living)	Off	25.7	(7.0)	26	(14–45)
	On	15.6	(6.8)	16	(3–34)

Of the 59 patients, seven (12%) died of causes unrelated to LCIG infusion after a time lag of 34.0 ± 28.4 (mean ± standard deviation) months (range 5–78 months) from the start of infusion at an age of 73.9 ± 4.0 years. The causes of death are listed in Fig. 1.

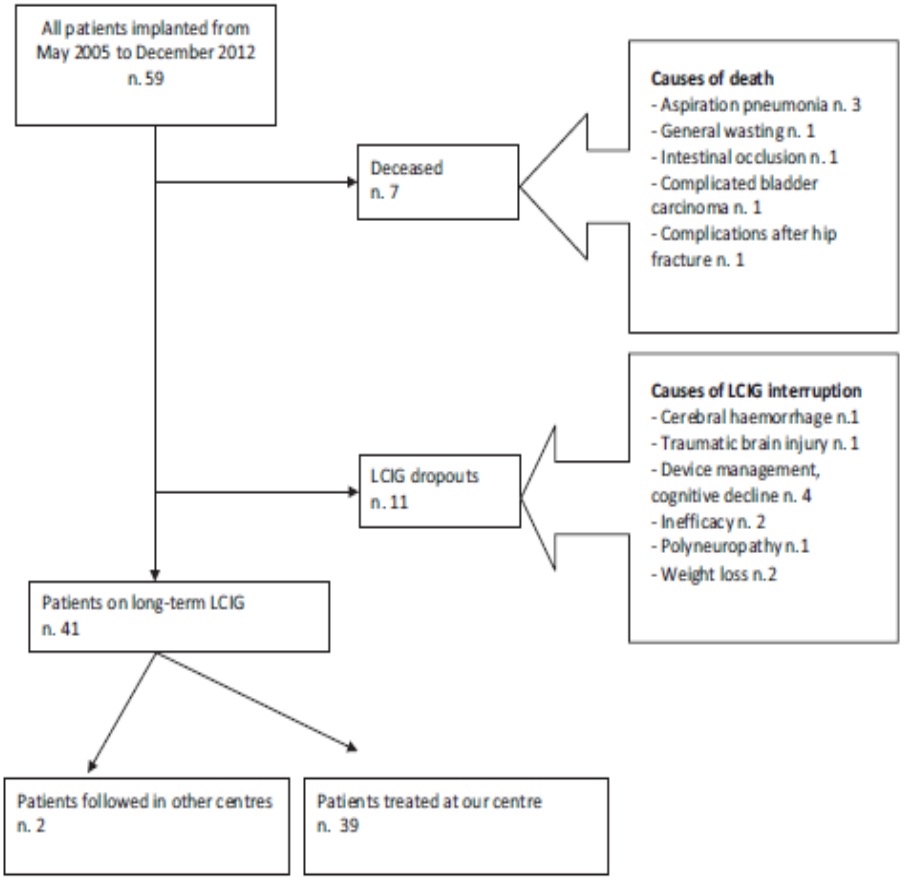

Figure 1 Flow chart of patients.

Eleven patients (19%) discontinued therapy prior to the cut-off date, after a time lag of 19.3 ± 14.9 months (range 3–56 months) from the start of LCIG. The causes of treatment discontinuation are shown in Fig. 1.

Deceased and dropout patients did not differ significantly from patients remaining on LCIG for any of the variables considered (age, age at PD onset, LCIG dose, disease duration at LCIG initiation, baseline UPDRS II, III and IV) except for sex (the proportion of females dropping out was significantly greater than the proportion of males; P = 0.044). Forty-one patients were still on treatment at the cut-off date, 31 December 2012. The mean ± standard deviation duration of LCIG treatment was 25.8 ± 19.5 months (median 19.0 months, range 3–87 months).

The efficacy of LCIG infusion in terms of QoL, autonomy and clinical global improvement was assessed in 39 patients. The perceived QoL improved in all patients. Autonomy and clinical global status improved in 90% of the patients. The majority of patients (54%) reported an improvement of gait, whereas dysphagia improved only in 33% and dysarthria in 18%. All patients required help from a caregiver in the management of the infusion device (Table 2).

Table 2. Efficacy of LCIG in terms of quality of life, autonomy and clinical global improvement, gait disorders, dysphagia and dysarthria and percentage of patients requiring help from a caregiver

Patients (n = 39)	Great improvement	Moderate improvement	Slight improvement	No change	Worsening
Quality of life	17 (44%)	19 (48%)	3 (8%)	0	0
Autonomy	12 (30%)	20 (51%)	3 (8%)	1 (3%)	3 (8%)
Clinical global improvement	24 (62%)	11 (28%)	4 (10%)	0	0

	Improvement	No change	Worsening
Gait disorders	21 (54%)	16 (41%)	2 (5%)
Dysphagia	13 (33%)	23 (59%)	3 (8%)
Dysarthria	7 (18%)	30 (77%)	2 (5%)
	Always	Sometimes	Never
Help from caregiver	25 (64%)	14 (36%)	0

Complications of therapy assessed by the UPDRS IV improved by 32% (P < 0.001); dyskinesia duration was reduced by 30% (P = 0.002), dyskinesia disability improved by 48% (P = 0.001) and painful dyskinesia improved by 78% (P = 0.020). Off-period duration was reduced by 49% (P < 0.001); unpredictable off-periods and sudden off-periods occurred in a significantly smaller proportion of patients (P < 0.001) whilst early morning dystonia and predictable off-periods did not change significantly (Table 3).

Table 3. Complications of therapy (UPDRS IV) for 39 patients at baseline and after a mean ± standard deviation of 25.8 ± 19.5 months (median 19.0 months, range 3–87 months) of LCIG infusion

UPDRS IV (Complications of therapy)	Range	Baseline	Follow-up	Percentage reduction	*P* value
Total score (items 32–42)	0–23	8.5 (3.1)	5.7 (2.4)	32%	**0.000**
Dyskinesias duration (item 32)	0–4	1.7 (0.9)	1.2 (0.7)	30%	**0.002**
Dyskinesias disability (item 33)	0–4	1.0 (1.1)	0.5 (0.7)	48%	**0.001**
Dyskinesia pain (item 34)	0–4	0.2 (0.5)	0.0 (0.3)	78%	**0.020**
Early morning dystonia (item 35)	0–1	13/39 (33%)	9/39 (23%)	–	0.219
OFFs predictable (item 36)	0–1	33/39 (85%)	34/39 (87%)	–	1.000
OFFs unpredictable (item 37)	0–1	26/39 (66%)	13/39 (33%)	–	**0.001**
OFFs sudden (item 38)	0–1	18/39 (46%)	2/39 (5%)	–	**0.000**
OFF state duration (item 39)	0–4	1.8 (0.7)	0.9 (0.5)	49%	**0.000**
Anorexia, nausea (item 40)	0–1	8/39 (21%)	9/39 (23%)	–	1.000
Sleep disturbances (item 41)	0–1	33/39 (85%)	31/39 (79%)	–	0.727
Orthostatic hypotension (item 42)	0–1	18/39 (46%)	12/39 (30%)	–	0.180

P values <0.05 are shown in bold characters.

The mean levodopa dose with oral treatment at the baseline was 1283 ± 434 mg/day (range 520–2458 mg). LEDD increased slightly at hospital discharge following LCIG initiation to 1453 ± 372 mg/day (range 510–2440 mg; P < 0.001) and remained substantially unchanged at the last visit with a value of 1506 ± 442 mg/day (range 552–2338 mg; P = 0.204) (Table 4).

Table 4. Concomitant medication used by 59 patients on long-term LCIG infusion

	Baseline	LCIG initiation	LCIG follow-up
LEDD	1282 ± 434	1453 ± 372*	1506 ± 442*
Evening levodopa dose	41 (69%)	42 (71%)	38 (67%)
Dopamine agonists	33 (56%)	4 (7%)*	9 (16%)*
COMT-I	27 (46%)	0 (0%)*	2 (3%)*
MAO-I	5 (8%)	1 (2%)	3 (5%)
Amantadine	7 (12%)	6 (10%)	9 (16%)
Antipsychotic	15 (25%)	22 (3 7%)*	21 (36%)*
Antidepressants	17 (29%)	17 (29%)	18 (31%)
Anxiolytics + hypnotics	39 (66%)	40 (68%)	43 (73%)

*P values < 0.05.

The mean continuous dose was 3.4 ± 1.0 ml/h at hospital discharge and 3.7 ± 1.1 ml/h at the last visit. LCIG infusion was performed for an average of 14.7 ± 0.8 h during daytime and was stopped at bedtime in all patients except one who infused 24 h (3.5 ml/h).

Duodopa was initially used as monotherapy in all but 11 patients (19%) for whom dopamine agonists (four patients) and amantadine (seven patients) were maintained. Extended release levodopa at bedtime was maintained in 34 patients (56%). At the last visit, 41 patients were on monotherapy with LCIG during daytime (72%). Dopamine agonists were given in association with LCIG in nine patients, oral liquid levodopa was given in association in seven patients, catechol O-methyltransferase inhibitors (COMT-I) in three, monoamine oxidase inhibitors (MAO-I) in three and amantadine in seven patients. Use of antipsychotics increased slightly from LCIG initiation to the last follow-up visit, whereas antidepressants, anxiolytics and hypnotics did not differ significantly from before starting LCIG infusion.

Adverse events related to the infusion devices were the most common complications, specifically intestinal tube dislocation, occlusion or kinking. Device problems were a contributing reason for the discontinuation of infusion in seven out of 11 patients (Table 5). In relation to gastrostomy, 14 peristomal infections, one phlegmon and one localized peritonitis occurred within 1 month from the procedure and all were successfully treated with antibiotic therapy. There were three cases of postoperative pneumo-peritoneum with spontaneous resolution, two cases of intestinal volvulus and two buried bumper syndromes. A gastric decubitus caused by the inner tube presented after 6 months from PEG-J placement and resolved with medical therapy and temporary removal of the inner tube. A case of duodenal perforation occurred after 1 year from the PEG-J placement and required surgical jejunostomy. Concerning LCIG infusion, there was an acute psychosis resolved with Duodopa dose reduction and neuroleptics, 10 cases of weight loss (≥10 kg) and four cases of polyneuropathy.

Table 5. Adverse events in 59 patients treated with long-term LCIG infusion

Adverse events	No. events	No. patients	No. events/patient/year
Related to infusion devices	83	55	0.65
Intestinal tube dislocation	36	29	0.28
Intestinal tube occlusion or kinking	28	16	0.22
PEG internal retention failure	12	6	0.09
Accidental external PEG damage	5	4	0.04
Possibly related to LCIG infusion	15	15	0.12
Severe psychosis	1	1	0.01
Important weight loss (>10 kg)	10	10	0.08
Neuropathy	4	4	0.03
Gastrostomy related	25	23	0.20
Peristomal infection	14	12	0.11
Phlegmon	1	1	0.01
Localized peritonitis	1	1	0.01
Pneumo-peritoneum	3	3	0.03
Intestinal volvulus	2	2	0.02
Buried bumper syndrome	2	2	0.02
Gastric ulcer caused by the tube	1	1	0.01
Jejunal perforation	1	1	0.01

Discussion

In this study a 7-year experience assessing safety and outcomes of LCIG infusion in 59 advanced PD patients presenting motor fluctuations and severe dyskinesia is described. Overall, our findings are in agreement with the first retrospective analysis of long-term use of Duodopa over a period of 11 years and support the conclusion that technical challenges posed by the enteral infusion system are offset by the improvement in motor fluctuations and dyskinesia [14]. In a series of advanced PD patients recently published reporting clinical outcomes over a 2-year period, there was a 25% withdrawal rate from LCIG, due to adverse drug reaction, procedure and device-related events, poor compliance and lack of efficacy [15]. This value is quite similar to the 19% dropout rate found in our cohort and the causes of treatment withdrawal were also similar. Amongst the factors possibly characterizing patients who discontinue LCIG treatment, a greater proportion of females in the dropout group was found, in agreement with the large follow-up study by Nyholm et al. [16].

Concerning the efficacy outcomes, similarly to the French Duodopa Study [12], 3- and 5-level scales were chosen despite methodological limitations. Ideally, it would have been better to have complete UPDRS assessment also at the follow-up; however, since many of the patients were unable to come to the clinic a telephone interview was arranged instead. Although the questions used are unbalanced, making an answer with a positive response to treatment more likely, patients, caregivers and neurologists were generally very satisfied. Most patients reported a great or moderate improvement of their QoL, autonomy and clinical global status. Despite this improvement, all patients required help in the management of the infusion device. A considerable proportion of patients (54%) reported an improvement in gait disorders, some patients reported an improvement of dysphagia (33%) whilst only a minority reported an improvement of dysarthria (18%) with LCIG infusion.

The majority of advanced PD patients are affected by motor fluctuations and disabling dyskinesia that lead to a substantial decline in QoL[17]. It is therefore of interest to analyse in detail the long-term outcome of motor complications in patients undergoing LCIG infusion. A 30% reduction of time spent with dyskinesia and a substantial reduction of debilitating and painful dyskinesia were found. A recent review has summarized the current efficacy and safety data for Duodopa, using clinically important differences (CIDs) to ascertain whether statistical improvements in symptoms translate into meaningful improvements for patients [7]. The CID refers to the 'amount of change on a measure that patients can recognize and value' and helps clinicians to distinguish between reported treatment differences that are relevant in clinical practice and those that are statistically significant but produce no recognizable benefit to patients [18]. The minimal CID for the UPDRS IV values was considered to be 0.7–2.3 points for the total score and 0.6–1.6 for the dyskinesia score (sum of items 32–35 of UPDRS IV) [19]. In this study the difference between the baseline levels and LCIG treatment was 2.8 points for the UPDRS IV total score, which exceeds the upper limit of the suggested CID value, and 1.1 points for the dyskinesia score, within the range of the suggested CID value.

Moreover, in the present study off-period duration was reduced by 49% and unpredictable and sudden off-periods both occurred in a significantly smaller proportion of patients. This could have a direct clinical relevance for LCIG-treated patients, since it has been shown that 'unpredictable-offs' have a negative impact on QoL [17]. On the other hand, early morning dystonia did not change significantly. This is predictable, based on the fact that LCIG was infused only during daytime waking hours and stopped at night. Most patients (67%) maintained an evening dose of extended release levodopa/carbidopa after stopping LCIG infusion. Only in one patient was LCIG infused continuously over 24 h because of an otherwise intractable debilitating nocturnal akinesia. As initially proposed by Nyholm et al. [20], this strategy seems to improve night-time motor performance and sleep quality without clinically meaningful tolerance.

Concerning the total levodopa dose infused daily, there was a slight increase (13%) at the first hospital discharge that was maintained substantially unchanged at the last evaluation. This confirms that levodopa daily dosage seems to be stable over the years as previously reported in the longest follow-up study of LCIG treatment yet published [16]. The concomitant pharmacological therapy was simplified with most patients suspending or reducing the dose of dopamine agonists, COMT-I and MAO-I. On the other hand, treatment with amantadine was mostly maintained in a minority of patients. At follow-up evaluation most patients used LCIG as monotherapy. As recently noted by Foltynie et al. [21], some of the beneficial effect of LCIG probably relates to the ability to provide more continuous plasma levels of levodopa, whereas other beneficial effects might well also relate to withdrawal of dopamine agonists.

Concomitant therapy for behavioural symptoms was substantially unchanged with the exception of neuroleptics that were given to more patients, possibly reflecting a progressive cognitive impairment.

Adverse events related to the infusion system were by far the most common, similarly to several other studies [7, 12, 13, 16, 19]. Surgery-related adverse events occurred less frequently, with infections and inflammations making up the majority of procedure-related adverse events; some serious complications related to gastrostomy occurred, amongst which was one case of duodenal perforation requiring surgical jejunostomy. The possibility of serious adverse effects highlights the importance of a multidisciplinary approach to LCIG treatment since the correct management of LCIG-related problems may demand gastroenterological, radiological and surgical expertise. LCIG centres should therefore provide respective adequate standards and an easy patient access to a dedicated therapeutic team [22].

Finally, in relation to LCIG infusion, several cases of weight loss requiring dietary integration and nutritional status monitoring were observed. In keeping with recent reports [23-25], four cases of polyneuropathy were also observed: one patient developed a severe subacute sensory-motor multineuropathy after 4 months of LCIG treatment and a decision was made to stop LCIG infusion, whereas three subjects with pre-existing mild polyneuropathy showed a worsening of electrophysiological and clinical features. LCIG treatment was not interrupted in these subjects, but vitamin B12 supplementation and strict clinical and electrophysiological monitoring was carried out. These cases are described in greater detail in a separate report on the prospective assessment of peripheral neuropathy in LCIG-treated patients recently published by our group [26].

In conclusion, this 7-year experience with LCIG continuous infusion in a cohort of 59 advanced PD patients confirms the validity of the treatment in the long-term management of motor fluctuations and dyskinesias, with a relatively low dropout rate mainly due to device-related problems.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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