Causes of withdrawal of duodenal levodopa infusion in advanced Parkinson disease

Daniela Calandrella, MD
Luigi M. Romito, MD, PhD
Antonio E. Elia, MD, PhD
Francesca Del Sorbo, MD
Caterina F. Bagella, MD, PhD
Massimo Falsitta, MD
Alberto Albanese, MD

Correspondence to Dr. Albanese: alberto.albanese@unicatt.it

ABSTRACT

Objective: We performed a real-life observation of patients with Parkinson disease (PD) who received duodenal levodopa infusion (DLI) to determine which adverse events caused treatment discontinuation and when such events occurred.

Methods: All consecutive patients with PD treated at the Carlo Besta Neurological Institute were included. The patients were evaluated at baseline and after DLI at regular intervals. Their motor condition was assessed and adverse events were recorded.

Results: Thirty-five patients with PD (15 men and 20 women) were included. They received DLI implants between October 2007 and September 2013. Four patients died of causes unrelated to the procedure. At the end of the study, 21 patients (60%) were still on treatment. DLI provided efficacious motor control in all patients. Discontinuation was most frequently caused by device- or infusion-related adverse events. Ten patients of the remaining 31 discontinued DLI. There were 2 main causes of withdrawal: stoma infection (4 patients), and worsening of dyskinesias not manageable with infusion reduction (3 patients). In most patients, discontinuations occurred during the first year after implant. Risk of discontinuation was related to age at implant, but no other demographic or clinical variables.

Conclusions: We identified 2 main causes leading to DLI withdrawal during the first year postimplant and suggest adopting measures to prevent such occurrences. Elderly patients are at higher risk of treatment discontinuation. *Neurology*® 2015;84:1669–1672

GLOSSARY

DLI = duodenal levodopa infusion; **LEDD** = levodopa equivalent daily dose; **PD** = Parkinson disease; **PEG** = percutaneous endoscopic gastrostomy.

Duodenal levodopa infusion (DLI) was first reported in the United States[1] and later implemented in Europe; it is currently approved in the European Economic Area, Switzerland, Canada, and Australia. This treatment requires applying an infusion device through a percutaneous endoscopic gastrostomy (PEG) to reach the duodenum.[2] Usually the infusion is performed during waking hours and stopped overnight; standards of care require daily hygiene and periodic intestinal tube replacement. European guidelines grant Level C recommendation to DLI for the treatment of severe motor fluctuations, dyskinesias, and biphasic dyskinesias.[3] Long-term data indicate that approximately 31% of patients with DLI discontinue therapy and that 17% die by an 8-year median treatment duration.[2] These figures raise some concern, particularly because the causes of withdrawal and death in patients with DLI treatment are still poorly known. We therefore performed a real-life study on patients with Parkinson disease (PD) who received DLI at the Carlo Besta Neurological Institute and determined which adverse events caused treatment discontinuation and the time of occurrence of such events.

We reviewed all consecutive patients with PD who received DLI since October 2006 and evaluated their status until June 2014. In all patients, DLI was administered as monotherapy during waking hours.[4] At night, the patients received extended-release levodopa or dopamine

From Neurologia I (D.C., L.M.R., A.E.E., F.D.S., C.F.B., A.A.), Istituto Neurologico Carlo Besta, Milano; Istituto di Neurologia (L.M.R., A.E.E., F.D.S., C.F.B., A.A.), Università Cattolica del Sacro Cuore, Milano; and Endoscopia Diagnostica e Chirurgia Endoscopica (M.F.), Istituto Nazionale Tumori, Milano, Italy.

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agonist supplementation. Before surgery, all patients were on multiple oral medications that were gradually changed to DLI during the first day after PEG. We analyzed in detail adverse events and causes of DLI withdrawal.

METHODS Inclusion criteria were diagnosis of idiopathic PD, excellent and sustained response to levodopa, severe motor fluctuations (prolonged and at least occasionally unpredictable *off*), at least 25% of the waking day spent in *off*, and occurrence of *on*-period dyskinesias. All the patients were Hoehn and Yahr stage ≥III in *off*, and had no cognitive or psychiatric abnormalities. All fulfilled the inclusion criteria set by the CAPSIT-PD (Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease) panel.[5] Age was not an exclusion criterion; some patients who did not consent to receive deep brain stimulation accepted DLI instead. A high level of personal and familial compliance was considered a prerequisite for inclusion.

Patients were evaluated at baseline and postoperatively at regular intervals. Preoperative evaluations were performed in *on* with a levodopa dose 50% higher than the usual morning dose of dopaminergic treatment. Postoperative assessments were performed in *on* with DLI. The levodopa equivalent daily dose (LEDD, measured in milligrams) was obtained in the preoperative state by adding to the standard levodopa dose all dopaminergic medications converted to the relative potency of standard levodopa.[6]

All patients received a PEG in a single center by the same endoscopist (M.F.). Two different systems were used over time for the PEG connection: the Flocare Bengmark tube (Nutricia Healthcare, Trowbridge, UK) was used for the first 5 patients; from 2008, the EndoVive TTP jejunal feeding tube (Boston Scientific, Spencer, IN) was used for the remaining 30 patients. In all patients, the tube was changed at yearly intervals.

Postoperatively, all patients received monotherapy with DLI. Dose optimization involved titration in step up to a minimum of 2 mg/h (0.1 mL/h) and a gradual decrease in case of dyskinesias.[7] The motor assessment was performed by means of the Unified Parkinson's Disease Rating Scale motor section: total score and 2 subscores for dyskinesia (sum of items 32 and 33) and *off* duration (item 39). Adverse events were recorded in all available detail and classified as transient or persistent. Surgery-related events were defined as adverse events related to the surgical procedure, including the first PEG and the periodic intestinal tube replacement; device-related events were defined as adverse events related to intestinal tube, stoma, or pump complications; and infusion-related events were adverse events related to delivery and administration of levodopa-carbidopa intestinal gel. Events not obviously related to these causes were classified as unrelated to procedure. Causes of withdrawal were annotated and linked to the causative event whenever possible.

Variables were compared by means of the Wilcoxon signed rank test. Survival and failure time analysis were performed using the Kaplan–Meier product-limit method. Survival time curves were also separately analyzed for patients who started DLI before or after age 70 years. Any p values <0.05 were considered statistically significant. All values were expressed as means ± SD. Statistical analysis was performed using StataSoft STATISTICA software (release 7.0; StatSoft, Inc., Tulsa, OK).

Study protocol approvals, registrations, and patient consents. The study was approved by the internal review board of the Carlo Besta Neurological Institute. Informed written consent was obtained from each patient.

RESULTS Thirty-five patients with PD (15 men and 20 women) were included. They received DLI implants between October 2007 and September 2013. The demographic and clinical features of these patients are reported in table 1. Dyskinesias and *off* duration were markedly reduced: the dyskinesia score by 31.8% ($p < 0.001$), and the *off* duration by 54.2% ($p < 0.001$). Unpredictable *off* and sudden *off* occurred in a significantly smaller proportion of patients after implant ($p < 0.001$). LEDD did not change after implant compared with baseline.

Table 1 Demographic and clinical features of the patients

	Baseline (n = 35)	Last visit (n = 21)
Age at disease onset, y	54.4 ± 9.4	
Age, y	64.8 ± 13.5	
Disease duration, y	12.3 ± 3.9	
Hoehn and Yahr stage	III–IV	III–IV
Sex, % female	57	57
Body weight, kg	63.3 ± 15.5	62.1 ± 13.6
DLI treatment, mo		32.3 ± 24.7
Daily DLI time, h		12.5 ± 0.9
Tube replacements		2.37 (1–7)
LEDD, mg	1,369.5 ± 499.4	1,484.3 ± 438.5
UPDRS motor score (part III)	36.5 ± 2.4	28.5 ± 5.0[a]
Dyskinesia score (UPDRS part IV items 32 + 33)	2.2 ± 0.7	1.5 ± 0.7[a]
Off duration score (UPDRS part IV item 39)	2.4 ± 0.6	1.1 ± 0.6[a]

Abbreviations: DLI = duodenal levodopa infusion; LEDD = levodopa equivalent daily dose; UPDRS = Unified Parkinson's Disease Rating Scale.
Data are mean values ± SD or mean values (range).
[a] Statistically different from baseline ($p < 0.001$).

Adverse events, causes of discontinuation, and deaths are reported in table 2. Discontinuation of DLI treatment was frequently caused by device- or infusion-related adverse events. Four patients died of causes unrelated to the procedure and are not further accounted for. Ten patients of the remaining 31 discontinued DLI for reasons related to the procedure (on average 11.3 ± 15.7 months after implant; range 0.4–48 months). The most common causes were stoma infection (4 patients, respectively, at 0.4, 0.5, 1.8, and 4.8 months postimplant), worsening of dyskinesias not manageable with infusion reduction (3 patients, 8.4, 9, and 12 months postimplant), duodenal perforation while replacing the DLI tube at a distant gastroenterology unit not expert on DLI implants (causing death in 1 patient 8.3 months postimplant), peritonitis (1 patient, 14 months postimplant), and duodenal phytobezoar (1 patient, 48 months postimplant).

In most cases, events causing discontinuations occurred during the first year after implant, in 89% of cases within the first 14 months (figure). Dropout patients did not differ from those who remained on DLI for any demographic or clinical feature. Dropout risk was correlated with age at implant, older than 70 years, and independent from any of the other variables considered (sex, age at disease onset, DLI dose, disease duration, baseline severity scores).

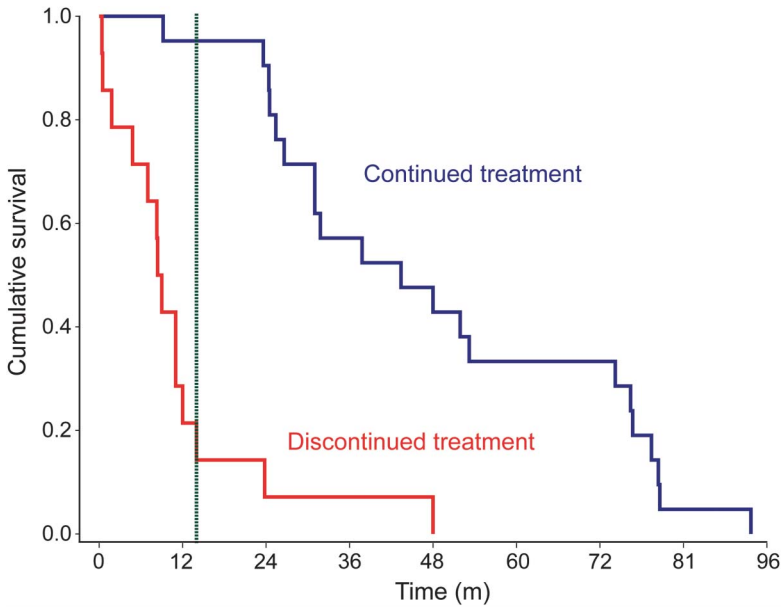
DISCUSSION We identified 2 main causes leading to DLI withdrawal during the first year postimplant: postsurgical stoma infection and worsening of dyskinesias. The first is a device-related event related to postimplant care and hygiene that occurred on average 3.3 ± 3.5 months after implant; better training of patients and caregivers may lead to reductions in this event. The second-most-common cause of withdrawal was dyskinesias that occurred on average 10.5 ± 2.1 months after implant. Worsening of dyskinesias has been previously reported to be a cause of withdrawal without specification of the time of occurrence[8]; the present observation indicates that some patients with a narrow therapeutic window do not attain an *on* state void

Table 2 Adverse events observed in patients with DLI treatment and number of patients who discontinued DLI

Events	Patients	Discontinued
Surgery-related		
Cardia bleeding	2 (7.5 ± 10.6 mo)	
PEG breakage	2 (41 ± 35.3 mo)	
Duodenal perforation when replacing tube	1	1[a] (8.3 mo)
Abdominal distention	1 (at first PEG)	
Atrial fibrillation	1 (at first PEG)	
Aspiration pulmonitis	1 (at first PEG)	
Stoma ulcer	1 (at first PEG)	
Device-related		
Stoma infection	5 (3.3 ± 3.6 mo)	4 (3.3 ± 3.5 mo)
Intestinal tube kinking	3 (10 ± 8.2 mo)	
Duodenal phytobezoar	1	1 (48 mo)
Intestinal tube loop/dislocation	3 (11 ± 11.3 mo)	
Peritonitis	1	1 (14 mo)
Infusion-related		
Worsening of dyskinesias	3	3 (10.5 ± 2.1 mo)
Peripheral neuropathy	1 (4 mo)	
Unrelated to procedure		
Accidental trauma	1	1[a] (23.8 mo)
Hepatocarcinoma	1	1[a] (11 mo)
Acute marrow aplasia	1	1[a] (11 mo)
Suicide (depression)	1	1[a] (7 mo)
Total	30	14 (5[a])

Abbreviations: DLI = duodenal levodopa infusion; PEG = percutaneous endoscopic gastrostomy.
Time of occurrence is reported in parentheses.
[a] Indicates death.

Figure Kaplan-Meier survival plot for patients with Parkinson disease receiving DLI



Patients who discontinued treatment are plotted separately from those who remained on DLI. The vertical line shows the 90th percentile for discontinuations, which includes 12 of the 14 patients who withdrew. DLI = duodenal levodopa infusion.

of dyskinesias in the early postimplant phase. Whether these patients belong to a distinct subset of PD is presently unknown. This observation has inevitable limitations because of the observational nature of the study design; notwithstanding, it may contribute to position DLI within the spectrum of device-aided therapies for advanced PD, whose indications are currently considered to overlap.[9]

We focus attention on the first year after implant and suggest that training of patients and caregivers and gentle changes in the infusion schedule may reduce the dropout rate. Programmed recalls during the first year after implant may be warranted. Furthermore, replacement of the infusion tube should be performed at centers expert on duodenal infusion and specifically knowledgeable on DLI.

AUTHOR CONTRIBUTIONS

Daniela Calandrella, Luigi M. Romito, Antonio E. Elia, Alberto Albanese: conception and design, analysis and interpretation of data. Daniela Calandrella, Luigi M. Romito: performed literature review and drafted the manuscript. Daniela Calandrella, Luigi M. Romito, Alberto Albanese: critically revised the manuscript for intellectual content and approved the final version to be submitted for publication. Francesca Del Sorbo, Caterina F. Bagella: performed clinical assessment of patients and acquisition of data. Massimo Falsitta: performed gastrointestinal assessment of patients and acquisition of data.

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DISCLOSURE

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