

## Long-term Outcome of Duodenal Levodopa Infusion for Advanced Parkinson's Disease

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### Abstract

Motor fluctuations and dyskinesias in Parkinson's disease (PD) patients cause severe disability and may not be adequately controlled by oral treatment. Long-term therapy options include deep brain stimulation (DBS) and apomorphine infusions. However, DBS is associated with neuropsychiatric complications and is suitable for only a small percentage of PD patients, and apomorphine infusion has no effect on dyskinesias and in our experience has a high drop-out rate. Infusion with levodopa on its own is not feasible as the drug is poorly soluble in water. In recent years, a novel gel form of levodopa plus carbidopa has been developed, enabling infusion directly into the duodenum through percutaneous endoscopic gastrostomy. Continuous levodopa infusion in this manner should

overcome the problems of fluctuations caused by pulsatile oral therapy. Our experience with Duodopa, reported here, includes 14 patients – nine of whom remained at two-year follow-up – and showed that, with continuous therapy, the total amount of levodopa administered to patients is relatively constant, and a therapeutic window could be established. The majority of adverse events were related to the procedure and hardware. Levodopa duodenal infusion improved motor fluctuations and reduced disabling dyskinesias, resulting in significant benefits in quality of life. Our results demonstrate that a satisfactory therapeutic window can be achieved and maintained for more than two years in advanced PD patients using this treatment. ■

There are many reasons why a clinical neurologist might be concerned about treatment of advanced Parkinson's disease (PD). Of the current options available, ergot-derived dopamine agonists can cause significant adverse events, such as impulse control disorders<sup>1-3</sup> and heart valve abnormalities;<sup>4-6</sup> apomorphine infusion is associated with skin reactions;<sup>7,8</sup> and deep brain stimulation of the subthalamic nucleus (STN-DBS), which is suitable for fewer than 3% of PD patients, is associated with behavioural and cognitive abnormalities<sup>9-11</sup> and does not improve quality of life in patients older than 65 years, who represent the majority of PD patients.<sup>11</sup>

### Long-term Treatment Options

STN-DBS has proved effective in providing significant clinical improvement in advanced PD patients. Indeed, STN-DBS is associated with a reduction in dopaminergic medications and 'off' time improvement. However, chronic use has been associated with a significant worsening of neuropsychiatric scales, resulting in long-term behavioural problems in some patients.<sup>11</sup> Moreover, this management option is not suitable for many advanced PD patients. A recent survey conducted in Italy attempted to establish the number of patients suitable for STN-DBS. Of 641 consecutive patients seen over one month, only 1.6% fulfilled the strict inclusion criteria of the core assessment programme for surgical interventional therapies in PD (CAPSIT-PD).<sup>10</sup> It is interesting to note that in this study 60% of patients were excluded because they failed to satisfy multiple criteria, while 20 patients were excluded for only one criterion. Criteria related to disease severity were responsible for the largest number of exclusions. By employing more flexible criteria – allowing patients with Unified Parkinson Disease Rating Scale (UPDRS) 'off' scores above 40, for example – the inclusion percentage can be raised to 3.7%. Including those with active psychiatric symptoms raised it to 4.5%. Therefore, while DBS is an interesting and relatively successful procedure, it cannot be applied in the large majority of cases.

Continuous dopaminergic stimulation (CDS) with apomorphine is not an ideal solution either. The 12-month effect of apomorphine infusion leads to improvement in off time, but does not improve dyskinesias as measured by the Abnormal Involuntary Movement Scale (AIMS). In comparison, STN-DBS results in greater reduction in dopaminergic medications and provides 24-hour motor benefit. However, unlike apomorphine, STN-DBS appears to be associated with significant worsening on the Neuro Psychiatric Inventory (NPI).<sup>11</sup>

Furthermore, experience of using apomorphine infusion at our clinic in Milan has not been as successful as other reports. In our experience, long-term apomorphine use is associated with a high drop-out rate and patients have not been able to stay on apomorphine for longer than three to four years. Complaints include appearance of skin nodules, receiving insufficient benefit and painful neck dystonia. In many cases the patients requested alternative treatments such as DBS or levodopa infusions. As with other dopamine agonists, long-term apomorphine use (around 24 months) was associated with impulse control disorders. These were reported in five patients and included one case of pathological gambling, two cases of addiction to the Internet, one compulsive eater with raised libido and one case of acute paranoia involving several suicide attempts, which eventually led to treatment being discontinued.<sup>12</sup>

### Effect on Non-motor Symptoms

Much of the attention on the effect of long-term treatments has been focused on motor symptoms. To balance this, the PaRkinson And nonMOtor symptoms (PRIAMO) survey is currently under way. This ongoing observational longitudinal study involves 55 Italian neurology centres with the objective of assessing the frequency of non-motor symptoms (NMS) in PD. Early results in 1,072 PD patients indicate that frequency of NMS is very high, particularly psychiatric symptoms.<sup>13,14</sup> However, as PD progresses the symptoms that become more common are not necessarily psychiatric, but tend to be related to urinary function, apathy, cognitive impairment and other neurodegenerative impairment (see *Table 1*). These symptoms must

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be taken into account when developing drugs with the aim of improving quality of life for advanced PD patients.

**Continuous Intra-intestinal Infusion of Levodopa–Carbidopa**

Continuous intra-intestinal infusion of levodopa–carbidopa might represent one of the best choices in these advanced patients. The hypothesis is that by making levodopa more stable in the plasma, NMS are more likely to be improved at the same time as dyskinesias.

Levodopa has poor solubility in water. Thus, the first intravenous infusions used large volumes of water, which is quite impractical.<sup>15</sup> The breakthrough came from the creation of a stable concentrated levodopa–carbidopa gel (Duodopa®), 100ml of which is equivalent to 3,000ml of water containing levodopa.<sup>16</sup> This 100ml cassette contains 2,000mg of levodopa and 500mg of carbidopa, enough for around 16 hours of infusion.

The intra-intestinal infusion of levodopa–carbidopa is typically divided into two phases. The first is a test period using a temporary nasal tube, which is not always necessary if the patient and his or her levodopa response is well known. There is, of course, no such test period available for DBS. However, it does help to familiarise the patient with the effect of CDS with Duodopa, and while in our experience transition to permanent Duodopa has occurred in 100% of patients, other centres have experienced patients taking the decision not to continue. The procedure to implant the catheter into the duodenum is via percutaneous endoscopic gastrostomy (PEG). Given that the tip of the catheter is lying in the duodenum and absorption of the compound is almost immediate, benefit can be seen very quickly from administration of Duodopa.

**Duodopa Experience**

The aim with CDS is to enable a patient who has been experiencing alternating ‘off–on’ dyskinesia to become more stable, able to walk and function throughout the day by reducing fluctuating plasma levels of levodopa. In Italy, 65 patients (age range 45–80 years) in 15 centres have been treated since June 2005. Of those centres, seven also perform DBS, but given the strict suitability criteria they cannot treat all patients.

Initially, at our centre in Milan the selection criteria for patients were quite strict and discussion is ongoing about the types of patients who are suitable for Duodopa. At our centre, 14 patients (six men, eight women) have so far been treated using the same CAPSIT-PD criteria as for DBS, but with no age limit. These include:<sup>12,17</sup>

- motor fluctuations and dyskinesia;
- Hoehn and Yahr (H&Y) stage >3;
- change of motor UPDRS score >30% between off and on states;
- no atypical features – such as falling, gaze abnormalities, autonomic dysfunction;
- no significant active psychiatric disturbances or dependence on antipsychotic drugs; and
- no dementia.

The key to the procedure is the gastroenterologist, who takes care of the practical part, including positioning the catheter and pump and adjusting medication.

**Table 1: Relationship Between Frequency of Non-motor Symptoms and Severity of Disease**

NMS	Disease Severity as Hoehn and Yahr Score			
	1	1.5–2	2.5–3	4–5
Pain	50.9	58.6	67.1	79.6
Urinary	43.1	51.7	68.3	89.9
Sleep dysfunction	47.9	60.6	75.4	81.6
Fatigue	37.7	56.5	68.9	81.6
Apathy	24.6	26.8	36.6	49.0
Loss of attention	37.7	40.4	51.7	65.3
Skin	14.4	19.8	34.5	32.7
Psychiatric	61.1	63.3	73.2	83.7
Respiratory	9.6	15.5	22.8	30.6
Gastrointestinal	45.5	54.4	76.9	73.5

**Table 2: Rating Scale for Duodopa Patients**

-3	Severe bradykinesia	‘Off’ state
-2	Moderate bradykinesia	
-1, 0, +1	Normal motor state	‘On’
+2	Dyskinesia	Hyperkinetic state
+3	Severe dyskinesia	

Table 2 shows the rating scale used for these patients during titration. This scale was based on a simplification of the UPDRS. There will be moderate bradykinesias and dyskinesias in the ‘on’ state, but these are judged not to be troublesome to the patient.

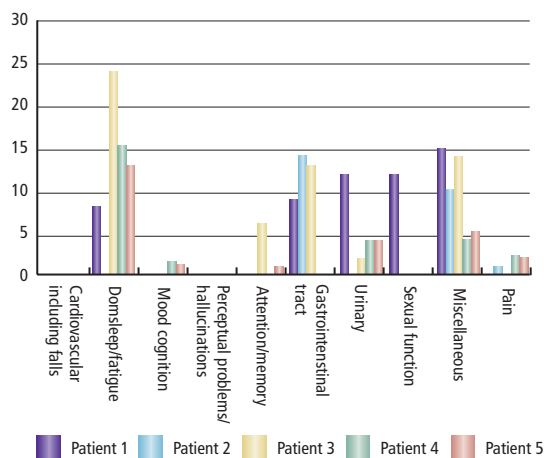
All patients started with the nasal tube before progressing to the permanent catheter. What was surprising was how quickly the patients stabilised, with most stabilising within the first week. In our experience it did not take long to find a therapeutic window in terms of the ‘on’

Given that the tip of the catheter is lying in the duodenum and absorption of the compound is almost immediate, benefit can be seen very quickly from administration of Duodopa.

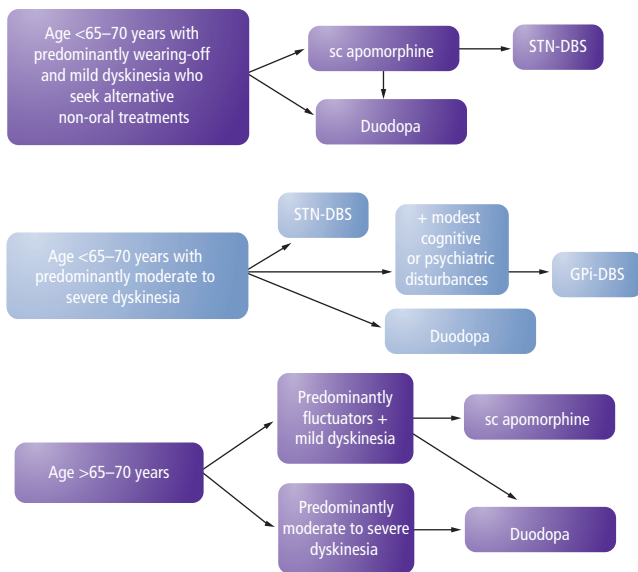
condition. Another important factor is that all patients were on combined levodopa and dopamine agonist treatment before the trial, but were switched to Duodopa monotherapy. This has implications not just from the patients’ point of view (improved compliance, reduced pharmaceutical burden), but also in economic terms.

There were nine patients at one-year follow-up – five men and four women with an age range of 50–80 years and disease duration from 12 to 25 years.<sup>17</sup> It is interesting to note that the total amount of levodopa administered via infusion did not differ from the dopaminergic oral treatments the patients were taking prior to the trial (in the region of 1,250mg/kg per day). Therefore, there is no need to change the dopaminergic drive in the patients; it is simply a matter of how they are administered. Patients were monitored from 8am to 10pm, and they had at least an 80% reduction in off periods and dyskinesias. These did not totally disappear owing to the small bolus injections in the morning and in the afternoon.

**Figure 1: Characteristics of Non-motor Symptoms in the Last Five Patients Enrolled on Duodopa Trial**



**Figure 2: Treatment Considerations for Different Types of Parkinson's Disease Patients**



sc = subcutaneous; STN-DBS = deep brain stimulation of the subthalamic nucleus; GPI-DBS = pallidal DBS; PD = Parkinson's disease.

In terms of overall quality of life, as measured by the Parkinson's Disease Questionnaire (PDQ-39), four domains showed significant improvement: bodily discomfort, stigma, activities of daily living and mobility. Other areas, such as emotional wellbeing and cognition, showed mild but not significant improvements.

Since the end of that trial, five new patients have been enrolled (three men and two women with an age range of 53–76 years). Two patients switched from combined levodopa and dopamine agonist therapy, while three moved from continuous apomorphine infusion. NMS changes are being specifically addressed in these five new patients, and patients' own perception of NMS is useful in judging the validity of the inclusion criteria for Duodopa.

Figure 1 shows that the most common complaints were related to urinary, gastrointestinal, fatigue and sleep problems. Very few patients mentioned mood/cognition, hallucination or perceptual problems.

Most complications were PEG-related, including one abdominal infection and four obstructed or broken PEG connections. Only two people dropped out – one for unrelated polyneuropathy and the other developed hallucinations after one month's treatment. Despite being free from hallucinations when the trial started, the latter had a history of hallucinations and psychosis.

## Summary

It is important to use strict patient inclusion criteria for optimal outcome with Duodopa. The hospital team that undertakes and monitors the procedure needs to be efficient, as the placement of the tube and the PEG involves a steep learning curve. The test period is also important.

Our findings confirm that levodopa by itself is not the cause of motor complications; rather, these are caused by the method of administration under oral therapy. A therapeutic window can be identified in advanced PD with severe motor fluctuations; such patients can benefit from Duodopa therapy. Moreover, the intra-intestinal infusion of levodopa-carbidopa resulted in a stabilisation of motor fluctuations after seven to 10 days, and dyskinesias and wearing-off improved considerably. Figure 2 shows the treatment options for different types of candidates. ■

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