

Continuous Duodenal Levodopa Infusion – The Barcelona Experience

a report by

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Abstract

Parkinson's disease (PD) is a highly debilitating, progressive disease that responds favourably to therapeutic doses of levodopa, the gold standard treatment for PD. Treatment of PD is largely determined by the phase of the disease the patient is currently experiencing: early, middle or advanced. Initially, there is good response to medication and adjuvant therapeutic strategies, but after six to eight years motor and non-motor complications develop. These are produced in part by erratic gastric emptying leading to irregular absorption and fluctuating plasma levels of levodopa, and hence an unstable response. At this point, clinical fluctuations are progressively more difficult to control and, consequently, the quality of life of patients deteriorates. The development of deep brain stimulation for the treatment of these long-term PD patients has been a major step forward. More

recently, a novel gel form of levodopa/carbidopa has enabled infusion through percutaneous endoscopic gastrostomy directly into the duodenum. This system avoids the gastric step, enhancing absorption of the drug and favouring stable plasma levels of levodopa. The advantages of this approach have since been considered in several clinical studies. In order to investigate the clinical effects of intraduodenal levodopa infusions on motor fluctuations and to explore the safety issues, we have conducted a multicentre prospective study in the area of Barcelona (Catalonia, Spain). The preliminary results of this study in 26 patients are presented here and discussed together with the recommended management, from our experience, of the most frequent adverse effects and mechanical complications of the infusion device that we have observed. ■

Our as-yet quite short experience with continuous levodopa infusion (Duodopa) therapy at the University of Barcelona began 18 months ago. We decided to include patients who fulfilled the following criteria:

- advanced idiopathic Parkinson's disease (PD);
- absence of associated diseases limiting survival;
- good response to levodopa;
- motor fluctuations;
- all available oral therapy exhaustively tested;
- absence of severe cognitive problems;
- absence of active psychiatric complications; and
- good support from family/care-givers.

Our contraindications, which are in common usage, were:

- glaucoma
- severe hepatic or cardiac insufficiency;
- cardiac arrhythmia;
- stroke;
- treatment with non-selective monoamine oxidase (MAO) inhibitors or MAO-A inhibitors; and
- pheochromocytoma, Cushing's syndrome and/or hyperthyroidism.

Objectives and Methods

The objective of the study was to analyse the efficacy and safety of continuous duodenal levodopa infusion in a subset of patients with advanced PD and severe motor fluctuations not optimally controlled with standard oral therapies. It was an open-label study with no group control and no blinded evaluations. Assessments were performed using the Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr (H&Y) staging and patient home diaries at baseline and at three-, six-

and 12-month follow-up. At the time of writing, only three patients have data beyond 12 months.

At the start of the trial, patients initially received continuous duodenal levodopa infusion through a nasoduodenal tube in order to test their response. Responders underwent a percutaneous endoscopic gastrostomy (PEG) to have the permanent tube inserted. During the recruitment period we processed 15 suitable candidates who had a nasoduodenal tube inserted. Thirteen of these accepted PEG. Those who did not accept PEG either had superior expectations that were not met by the preliminary infusion or experienced hallucinations during this testing phase (see *Figure 1*).

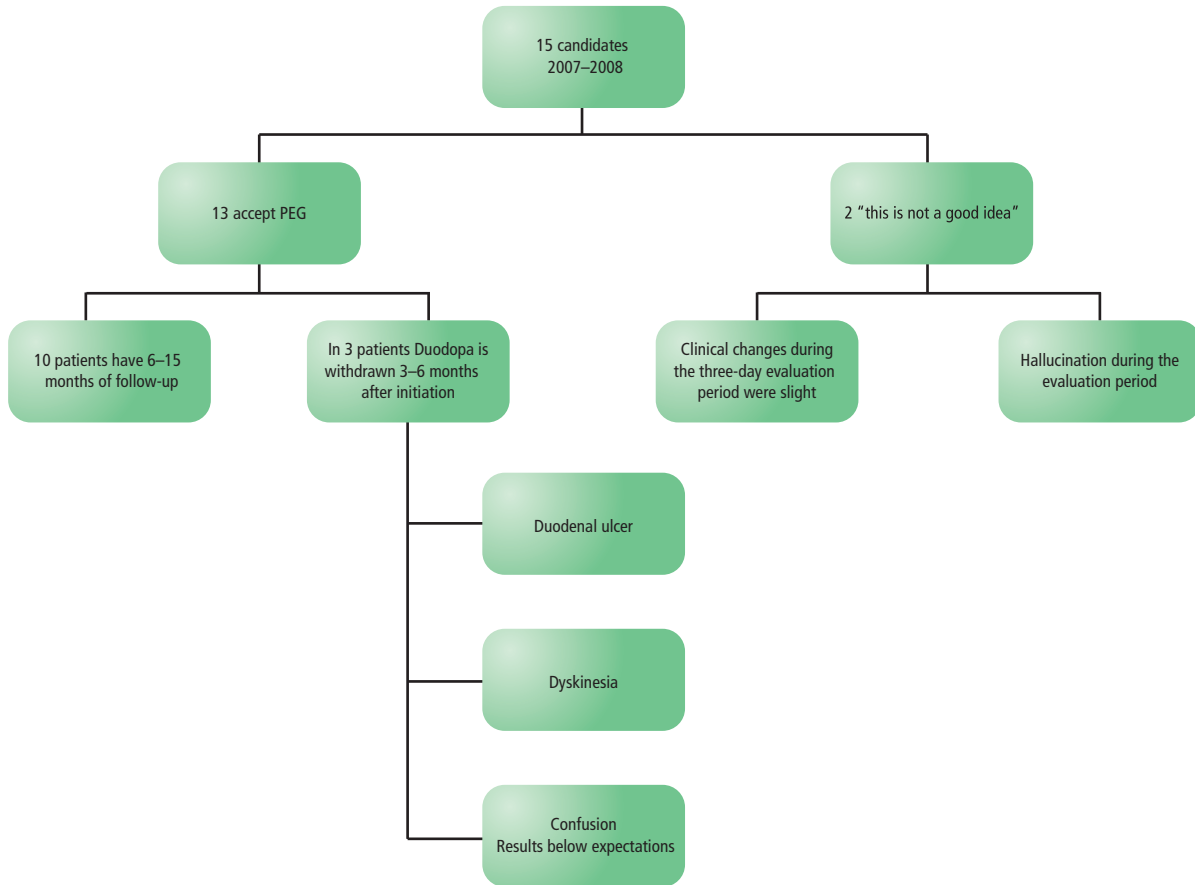
Table 1 shows the clinical characteristics of all 15 patients initially recruited into the trial. The age of the cohort is particularly interesting as it is on average slightly higher than would be expected with candidates for deep brain stimulation (DBS), and similarly the disease duration was longer. All patients were already on high doses of levodopa (>800mg/day) and seven patients had received previous surgery: DBS and/or pallidotomy. Off time was prolonged in all but one subject, at more than 50% on average.

Comparison with Previous Work

For the purpose of comparison, the closest study of Duodopa to our own that can currently be found in the literature is the paper by Antonini et al., in which disease duration and pre-study levodopa doses are both quite high – similar to those in our cohort.¹ The main difference is that

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Figure 1: Candidates in the Barcelona Trial



the Italian team made their measurements of off time and dyskinesia in minutes; nevertheless, they are still high and comparable to ours. A high pre-study levodopa dose is also seen in other Duodopa studies, for example the one undertaken by Nilsson et al.² However, comparing this with the Italian study, the Swedish researchers found that with continuous infusion the daily dose of levodopa effectively decreased, which the Antonini et al. study did not find.

Sweden is also the home of another benchmarking study, published in 2003. The patients included in this study were of a marginally lower average age and, apart from four out of 12 patients, had a comparable duration of therapy: the four outliers had a therapy duration of four to eight years.³ Furthermore, the patients had a lower percentage of off time than those in either our study or the Italian one.

Preliminary Results

So far only nine patients have completed the full 12 months of follow-up. Nevertheless, we believe that their results are representative of the overall trends. They are striking results: an 85% reduction in off-time and a 52% reduction in dyskinesias (see Figure 2). Our reduction in off time compares favourably with the 89% reduction obtained by Antonini et al. over a similar time period. However, the Italian team had a better overall reduction in dyskinesias at 74% compared with our 52%.¹

We tested the severity of the dyskinesias using the UPDRS. Prior to treatment, patients had dyskinesias on average 50% of the time, although they were not terribly severe: baseline level was just less than

1.4. They became even less severe after levodopa infusion, dipping below 0.6 at six months. Activities of daily living (ADL) also improved, although by a smaller proportion: the mean UPDRS score fell from 11 pre-treatment to a low of 7 at six months. Both ADL and dyskinesia score rose slightly between the six- and 12-month follow-ups.

In contrast to the results obtained by Nilsson et al.,² but in line with those from Antonini et al.,¹ we found that the equivalent daily dose of

Most patients reported improvement in nocturnal sleep (with continuous levodopa infusion), even with infusion stopped at bedtime.

levodopa increased when moving from oral therapy to continuous infusion. It must be considered that part of the reason for this is that the patients are now on monotherapy rather than polypharmacy. Nevertheless, the average daily levodopa dose rose by approximately 20% over the course of the year.

Complications

In terms of complications, there were three related to the device, eight

Table 1: Pre-Duodopa Clinical Characteristics of Patients

| Patient | Gender (M/F) | Age (years) | Disease Duration (years) | Levodopa-equivalent (mg/day) | Previous Surgery? | Daily 'Off' Time (%) |
|-----------|--------------|-------------|--------------------------|------------------------------|-------------------|----------------------|
| 1 | M | 74 | 12 | 1,940 | – | 60 |
| 2 | M | 64 | 14 | 905 | – | 75 |
| 3 | F | 65 | 24 | 1,790 | DBS + pallidotomy | 75 |
| 4 | F | 66 | 7 | 2,030 | – | 81 |
| 5 | M | 74 | 9 | 2,390 | – | 75 |
| 6 | M | 68 | 24 | 1,270 | – | 75 |
| 7 | M | 65 | 28 | 800 | DBS + pallidotomy | 40 |
| 8 | M | 71 | 16 | 1,645 | – | 60 |
| 9 | M | 68 | 27 | 1,860 | – | 50 |
| 10 | M | 62 | 22 | 1,000 | DBS | 40 |
| 11 | M | 67 | 19 | 1,490 | – | 44 |
| 12 | M | 74 | 12 | 2,440 | Pallidotomy | 31 |
| 13 | F | 73 | 15 | 1,460 | DBS | 19 |
| 14 | F | 57 | 17 | 1,500 | Pallidotomy | 40 |
| 15 | F | 75 | 18 | 1,500 | DBS | 60 |
| Mean ± SD | 5F/10M | 68.5±4.2 | 17.6±6.8 | 1,600±529 | – | 56 |

DBS = deep brain stimulation; SD = standard deviation.

related to the PEG procedure and 10 associated with levodopa. Three patients pulled out three to six months into the study: one with a case of digestive bleeding due to duodenal ulcer, one because of severe biphasic dyskinesia and one because of confusion combined with results being below expectations. As for the PEG-related complications, one patient experienced abdominal pain, four had an infection in the stroma and one developed a granuloma.

Continuous levodopa infusion is an effective therapy to reduce daily off time in advanced PD.

Complications related to levodopa included three cases of confusion; two were transitory, but one was severe enough to cause the patient to withdraw (as already discussed). Three patients experienced hallucinations that could be managed with quetiapine (one patient) or a reduction in levodopa dose (two). Six patients experienced a transitory increase in dyskinesia, including three cases of biphasic dyskinesias, which will be discussed later in this paper.

The pump and tubing caused a few complications. In one patient the inner tube migrated: it became disconnected from the device and travelled through the gut to be defecated. While this occurrence was ultimately without risk, it was a difficult situation to identify and explain to the patient. The inner tubes of three other patients developed loops and kinks, and five patients sustained damage to the external connectors.

Additional Observations

We observed other phenomena during the trial. Most patients reported improvement in nocturnal sleep, even with infusion stopped at bedtime. Two patients required 24-hour infusion in order to

improve sleep quality. This was well tolerated, and no tolerance phenomena were observed.

There was a low incidence of psychiatric complications among the patient population. It is likely this was helped by the total withdrawal of dopamine agonist therapy, which also explains the absence of compulsions such as punding, hypersexuality and compulsive shopping. Interestingly, we also observed improvement of non-motor fluctuations, particularly anxiety and pain.

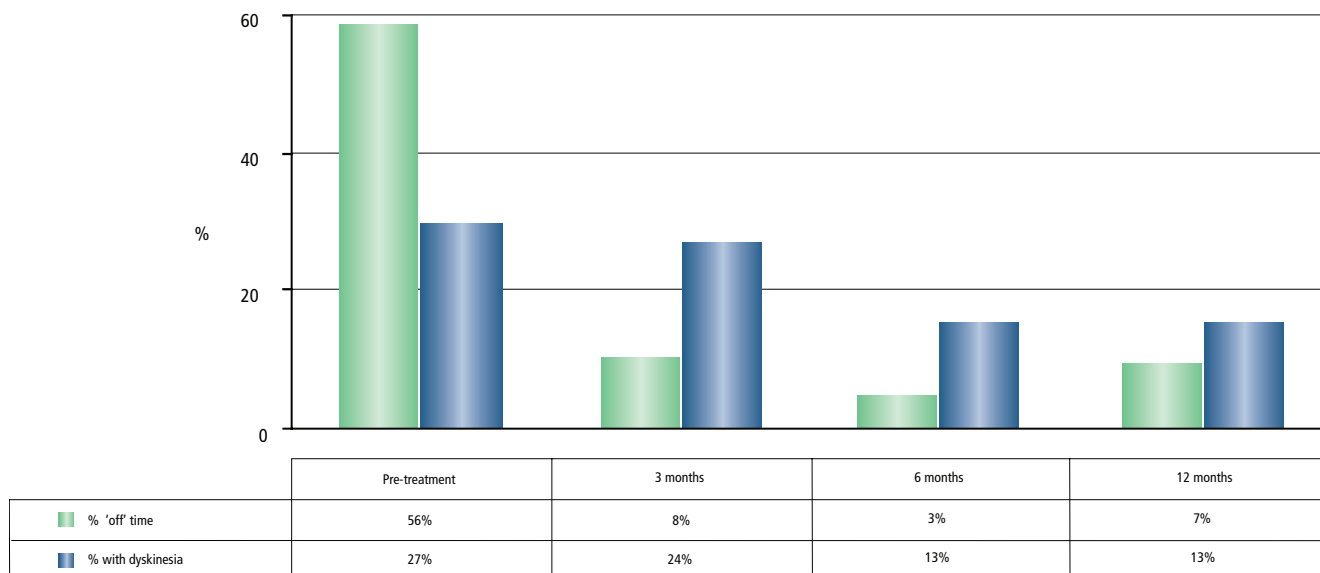
Biphasic Dyskinesias

We observed the phenomenon of biphasic dyskinesias in four patients. They were characterised by severe, painful, rhythmic movements of the legs that were difficult to manage. These were of new onset: patients did not suffer before the infusion. The biphasic dyskinesias were observed immediately after the Duodopa pump was switched off at bedtime or when the cartridge was changed. This indicates that these dyskinesias are directly related to a dip in plasma dopamine levels. Extra doses of levodopa, which can be initiated by the patient, helped to reduce the dyskinesias, although they could not be completely relieved. In contrast, lowering the infusion dosage caused the biphasic dyskinesias to worsen.

Other forms of continuous dopaminergic stimulation include apomorphine infusions and DBS. There is a comparative study of these two approaches: patients who underwent DBS did not suffer from more dyskinesias post-procedure, while those on apomorphine did. However, there is some confusion in the literature: some studies conclude that dyskinesias improve completely,^{4,5} while others say that apomorphine infusions have no effect.⁶ In our experience, according to home diaries written by patients and care-givers, patients operated on using DBS had significantly reduced dyskinesia, while patients infused with apomorphine appeared to worsen.

The previous literature on Duodopa documents a marginal improvement in the hyperkinetic state, with several patients showing substantial improvement compared with others who do not.² Other work, also from Uppsala, has used a control group fitted with dummy PEG tubes. These researchers observed a modest improvement in

Figure 2: Results – Motor Fluctuations and Dyskinesias



dyskinesias, but as the total proportion of dyskinesias during the day was small they were difficult to analyse accurately.⁷ Conversely, Stocchi et al. found significant improvement in dyskinesias after levodopa infusion.⁸

Indications versus Deep Brain Stimulation

Continuous levodopa infusion is, in many ways, competitive with DBS. However, in our experience advanced disease is not a critical or limiting factor in the treatment decision. Patients with some residual parkinsonian symptoms while 'on' can still be accepted as candidates. Similarly, patients of advanced age can still be suitable, as discussed in the article by Patricia Limousin. Furthermore, Duodopa has the advantage of being 100% monotherapy, which is of particular benefit for older patients who may suffer from psychiatric symptoms. Neither is Duodopa contraindicated in patients with structural brain problems that would render DBS unadvisable. For both treatments, it is critical that the patient has good support from his or her care-giver and good social support in general.

Severe dyskinesias could be a limiting factor for Duodopa. While continuous dopaminergic stimulation should improve both motor fluctuations and dyskinesias, our previous experience with subcutaneous continuous infusion of apomorphine showed that dyskinesias were a limiting factor for therapeutic success.

Collaborative Study

The collaborative Barcelona study of Duodopa includes patients from three hospitals in the area. This is a total of 27 patients (10 men, 17 women) with

a mean age of 66 years (range 54–76 years). Of the 27 patients, 24 were considered good responders after the period with nasoduodenal tube. The mean follow-up was 13 months (range three to 25 months).

Results

With Duodopa, average off time decreased from 63 to 12% ($p < 0.005$), leading to better control of motor fluctuations. On time with dyskinesias and H&Y stage did not change significantly from baseline. Total UPDRS scores while on improved by 15.3 points ($p < 0.05$), indicating that on time was of better quality. In patients still suffering off periods, total UPDRS scores improved by 61% ($p < 0.005$), indicating that they were less troublesome. Overall, the differences between on and off periods lessened.

The most frequent adverse effects related to technical problems with the infusion device ($n=9$), psychiatric complications ($n=8$) and, once again, the troublesome biphasic dyskinesias ($n=3$), but only four patients abandoned the treatment because of adverse events. In total, 20 patients are still receiving Duodopa.

Summary and Conclusions

Continuous levodopa infusion is an effective therapy to reduce daily off time in advanced PD. Adverse effects are generally related to the infusion system or are pharmacological complications that, in general, can be easily managed. In some instances, new biphasic dyskinesias have started to manifest when the pump is switched off. Sometimes these can be managed with an additional bolus of levodopa. They have not caused any patients in our cohort to abandon treatment. ■

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