

Applicability and Benefit of Enteral Levodopa/Carbidopa Infusion in Advanced Parkinson's Disease

a report by

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Parkinson's disease (PD) is a devastating, progressive disorder that responds favorably to therapeutic doses of levodopa, its gold standard therapy. The phase of the disease (early, middle, or advanced) largely determines the type of treatment. Initially, there is good response to medication and adjuvant therapeutic strategies but, after several years, motor and non-motor complications develop. These are produced in part owing to erratic gastric emptying, leading to irregular absorption and fluctuating plasma levels of levodopa, and hence an unstable response. At this point, clinical fluctuations are gradually more difficult to control and, therefore, patients' quality of life deteriorates. In recent years, the development of subthalamic and pallidal deep brain stimulation (DBS) for the treatment of these long-term PD complications has been a major step forward. There is good evidence that DBS can reduce the difference between off and on states and that the benefit achievable with DBS can be predicted by the levodopa response. Nevertheless, the clinical reality is that DBS does not reach the theoretical maximum effect in everyone. Patient selection and electrode location have a huge impact on the outcome, as does the experience of the surgeon. Adverse effects derived from the neurosurgical procedure are uncommon, but the so-called hardware complications produced by fractures, disruptions, or infections of the implanted system are relatively frequent. Psychiatric symptoms after subthalamic stimulation have also been repeatedly described in the medical literature. Moreover, a recent study demonstrated that only about 1.6–4.5% of patients are suitable for DBS.¹

In recent years, a novel gel form of levodopa/carbidopa (Duodopa®) has enabled infusion through percutaneous endoscopic gastrostomy (PEG) directly into the duodenum. This system avoids the gastric step, hence enhancing absorption of the drug and favoring stable plasma levels of levodopa. Duodopa has been approved in all EU countries plus Norway, Switzerland, and Canada. This is a treatment system for people who are in an advanced stage of the disease. Dosing of Duodopa is adjusted to the needs of each individual patient and is delivered continuously throughout the day. Duodopa is used as monotherapy. This method of continuous dopaminergic stimulation may give better control of the symptoms compared with traditional oral medication. It is given inside the upper intestine via a small tube inserted directly into the first part of the small bowel, or duodenum. The unique delivery system, with a programmable pump, allows the physician and patient to individually tune the delivery of active ingredients, suspended as stable gel from a cassette worn outside the body. Better control of body movements can be achieved, resulting in many patients becoming more functional in their daily lives. The advantages of this approach have since been considered in several clinical studies.

A three-week open, randomized, cross-over study comparing the variability in plasma concentrations of sustained-release levodopa and Duodopa infusion in 12 patients with motor complications showed marked improvement of fluctuations and increased on-time without dyskinesias during the infusion.² Another study³ demonstrated increased on-time (mean 4.5 hours); situations of moderate to severe parkinsonism virtually disappeared in patients who received the infusion compared with those who were treated with optimized oral medication.

Several studies of long-term effectiveness have also been published. In a retrospective open study,⁴ 28 patients with early onset of the disease and prolonged time of evolution were treated with Duodopa for up to seven years. The reason for infusion was in all cases related to motor fluctuations. The average daily intake of levodopa was reduced slightly by infusion compared with oral therapy. At the end of the study, continuous infusion continued to maintain the benefit with respect to the oral therapy in terms of increased on-time. Another retrospective long-term study⁵ was conducted through a structured review of medical records of all patients who had received enteral carbidopa/levodopa infusion during the period 1991–2002. All patients had advanced PD with dyskinesias and motor fluctuations. About 75% of patients remained in enteric infusion of levodopa for at least two years, with about 50% receiving infusion for at least six years.

Several prospective studies have also evaluated the efficacy of this therapy: an Italian survey⁶ on nine patients with advanced PD showed a remarkable reduction of the duration of the off-periods and important amelioration of disabling dyskinesias. Activities of daily living scores markedly improved; quality of life, as measured through standard scales such as the PDQ-39 (specific for PD), was also ameliorated in all patients.

Furthermore, a survey in five patients showed the usefulness of duodenal infusions during the night hours in patients with severe nocturnal Parkinsonian symptoms. Tolerance phenomena or increase of the occurrence of dyskinesias and hallucinations were not observed.



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The author and colleagues have observed striking results with the use of this therapy. They have prospectively evaluated 13 patients during a mean follow-up of one year. The off-time was reduced by a remarkable 85%; in addition, a moderate reduction in the duration and severity of dyskinesias was observed in patients averaging 50% of the waking day with dyskinesias prior to the intraduodenal infusion. Activities of daily living also improved. 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 and nocturnal mobility. There was a low incidence of psychiatric complications; it is likely this was helped by the total withdrawal of dopamine agonist therapy, which also explains the absence of other hyper-dopaminergic behaviors such as punding, hypersexuality, or compulsions. Interestingly, improvement of non-motor fluctuations was observed, particularly anxiety, pain, and vegetative symptoms. Improvement of non-motor symptoms has also been observed by others.⁷

Although serious adverse effects are not frequent, the existence of technical problems and complications related to the infusion pump and the enteric tube are well recognized. Most common problems are derived from the PEG and failures in the infusion system, thereby resulting in an increase in endoscopic and radiological procedures to correct the problems. In one survey,⁵ a majority of patients required additional endoscopic procedures after the initial gastrostomy; the rate of adverse events related to problems with surgery and the device was, on average, 1.8 incidents per patient per year. Dislocation of the tube from the small intestine to the stomach was a frequent complication. These problems are the reason for stopping treatment in an important proportion of cases. Other adverse effects result from the dopaminergic effect of the infusion and are not very different from those observed with the conventional oral therapy. Autopsies were performed in seven patients who died without observation of the existence of pathological changes in the gastric wall, duodenum, or jejunum.⁵ In the author and colleagues' experience, the most frequent complications were also related to problems with the duodenal tube such as kinking, migration of the inner tube or damage in the infusion pump. Dyskinesias were also seen in some patients, but most patients improved after dosing adjustments.

Enteral levodopa infusion has been implemented in patients with advanced PD and motor complications resistant to oral therapies. Duodopa infusions have been demonstrated to be effective in reducing the off-time in retrospective and prospective studies. All of them are non-randomized series with open evaluations in a small number of patients with short follow-up periods. Consequently, the amount of scientific support concerning the clinical effects of this therapy provides only class III and IV evidence. There are no published studies determining whether or not there is a specific profile of patients who might be ideal candidates, although some authors suggest that patients with prior psychiatric disorders are not good candidates for this therapy. Continuous levodopa infusion is, in many ways, competitive with DBS.

There are currently no comparative studies of any kind that directly evaluate the efficacy and safety of levodopa enteral infusions compared with DBS and, thus, there is no scientific evidence favoring the use of one or the other therapy.

In the author and colleagues' practice, patients showing symptoms that were non-responsive to dopaminergic agents, such as freezing of gait or dysarthria, which dominate advanced phases of the disease, are not good candidates for DBS. However, these patients could be challenged with Duodopa in order to improve motor fluctuations. Mild to moderate cognitive impairment could be accepted in candidates for enteral levodopa infusions, while it is a serious limiting factor for DBS. Advanced age is also an important restrictive feature for DBS, but not for duodenal infusions of levodopa. A low incidence of psychiatric adverse effects was found with enteral levodopa infusions. It is not contraindicated in patients with structural brain damage that could make DBS inadvisable. Obviously the surgical risk is less important with the PEG than with the implantation of electrodes for DBS. Care-giver support is equally important for success in both therapies. Both are complex therapies and are a full-time job for a team of physicians, although the technical requirements are less demanding for levodopa infusions than for neurosurgical procedures. On the other hand, in the author's experience, those patients presenting severe dyskinesias in the absence of other contraindications for brain surgery could probably take more benefit from DBS.⁸ In addition, Duodopa is not indicated in patients with established dementia and previous abdominal surgery.

Other therapies trying to achieve continuous dopaminergic stimulation include apomorphine infusions. Some comparative studies of these two approaches have demonstrated that patients who underwent DBS did not suffer dyskinesias after surgery, while those on apomorphine did.^{9,10} However, other studies conclude that dyskinesias improve completely after apomorphine infusions.^{11,12} In previous experience, according to home diaries patients on DBS significantly reduced dyskinesia, while patients infused with apomorphine appeared to worsen.¹⁰

In summary, continuous levodopa intraduodenal infusion is a useful therapy to reduce daily off-time in advanced PD. The procedure is, in general, well tolerated and complications are related to the infusion system and dopaminergic effects but can be easily managed. New clinical trials using blinded evaluations and control groups are needed to obtain the essential scientific support for this new treatment. However, at present and based on our own experience, Duodopa can be considered as a helpful tool for the management of otherwise untreatable problems associated with advanced PD.

Unfortunately, this therapy, like any other currently available therapy, is effective only in the treatment of the dopaminergic symptoms. The development of new therapeutic approaches facing the non-dopaminergic symptoms associated with advanced PD is urgently awaited. ■

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