

Treatment with Levodopa/Carbidopa Gel (Duodopa®) in patients with Parkinson's disease

*DANMODIS; Danish Movement Disorder Society
SWEMODIS, Swedish Movement Disorder Society*

Background

The first studies of intravenous and intraduodenal infusions of levodopa utilized water solutions. The chemical properties of levodopa and carbidopa require large volumes of water for the preparation of one day's supply, which made the method laborious. This problem was resolved with the development of a levodopa/carbidopa gel (Duodopa®, Solvay Pharmaceuticals GmbH, Hannover, Germany). By using a carboxymethyl-cellulose gel, the concentration of levodopa is 20 mg/mL, thus a cassette containing 100 mL is a sufficient daily dose for most patients. The cassette is attached to a portable pump (CADD-Legacy-Duodopa, Smiths Medical, MN, USA). The tube of the cassette is connected to a PEG (percutaneous endoscopic gastrostomy) tube, containing a smaller-bore intestinal tube, which is placed beyond the pylorus to allow for immediate absorption across the intestinal mucosa in the duodenum or proximal jejunum. The clinical response can be tested before establishing a PEG, by temporary Duodopa treatment through a naso-jejunal tube.

Indications for treatment with Duodopa

General indications

- Treatment of Parkinson's disease in the advanced and complicated phase, with motor fluctuations and/or hyper-/dyskinesias despite optimized oral/patch treatment
- Sufficiently severe symptoms to necessitate advanced treatment.

Special situations that may be successfully treated

- Long and/or frequent "off" periods and/or severe dyskinesias in spite of optimized oral therapy
- When treatment of advanced symptoms by means of deep brain stimulation (DBS) is contraindicated, ineffective or otherwise unsuitable
- When treatment of advanced symptoms by means of continuous subcutaneous infusion with apomorphine/dopamine agonist is contraindicated, ineffective or otherwise unsuitable
- Elderly people, as there is no age limit.
- Duodopa treated patients with a severe sleep disturbance that is unresolved by oral therapy, as the patient may benefit by extending the pump treatment to 24 hrs.

Other prerequisites

- The patients should have a clinical response to L-dopa
- Cognitive impairment, among other things, may require a care-giver assistance in a daily handling of the equipment, e.g. starting and stopping the pump
- A well planned setting in terms of logistics and support with regular, scheduled check-ups is necessary for successful treatment. A dedicated Parkinson team at a university hospital should be involved in initiating the treatment
- Adequate in-ward training of patients and care-givers must be provided

- Ideally, specialized PD nurses should be available for training, consultation and general education of patients and care-givers
- Each patient should have a tailor-made “optimal” peroral treatment schedule in case of interruptions in the Duodopa treatment due to problems with the pump or tube

Contraindications

- Hypersensitivity to levodopa or carbidopa
- Glaucoma
- Serious liver and kidney disease
- Severe heart failure
- Severe cardiac arrhythmias
- Recent or acute stroke
- Contraindications for adrenergic effects; pheochromocytoma, hyperthyroidism, Cushing’s syndrome
- Contraindications for abdominal surgery.

Relative contraindications

- Significant dementia, which makes the treatment more difficult to perform and leads to less favourable outcomes
- Ongoing treatment with unselective MAO inhibitors or selective MAO-A inhibitors (to be withdrawn at least 2 weeks before the start of treatment)

Start of treatment

The initial dosage of the levodopa/carbidopa gel is calculated on the basis of the previous dose of oral levodopa or levodopa equivalents. The continuous dose is normally between 20 and 120 mg/h. An individual morning bolus, usually 40-200 mg levodopa, is used to rapidly achieve steady-state, after which the concentration can be kept constant by the individualized infusion rate. Both morning dose and infusion rate are fine-tuned over the course of a few days in order to find the optimal dose that produces a continuous “on” state without troublesome dyskinesia. An extra bolus dose on demand is possible. As the bolus dose is titrated, 20-40 mg is usually sufficient. The infusion rate can be adjusted in small increments of 2 mg/h. The patient is discharged from hospital when the PEG surgery has been performed, an optimal dose found, and the patient or a relative has learned how to operate the infusion system, which usually takes about a week. Follow-up should be carried out by a PD nurse or at an outpatient visit a few weeks later. The dosage may need to be adjusted after some weeks to months, probably due to long-term plastic changes in the brain. The levodopa/carbidopa infusion has mostly been used as monotherapy, which is practical. If necessary, it can be combined with other anti-parkinsonian drugs, especially for “non-dopaminergic” symptoms. Initially the treatment is only administered during the day, and a long-acting L-dopa preparation and/or peroral dopamine agonist is given at bedtime. 24-hour therapy can be considered for patients on daytime therapy, who suffer significant sleep disturbance due to Parkinson symptoms.

Special circumstances

Levodopa plasma concentrations are smoothed, which probably accounts for the clinical effect. It is noteworthy that improvement can be seen in dyskinesias and dopaminergic side effects observed in spite of an unchanged or even increased total daily L-dopa dose. Psychotic side effects due to dopaminergic stimulation can improve. In many cases the total dose of

levodopa remains high or is even increased with Duodopa, leading to a considerable reduction in the frequency of fluctuations, hyperkinesias, and falls, as well as improved gait without increased rates of nausea, orthostatic hypotension or hallucinations.

A few patients received Duodopa via a percutaneous jejunostomy tube.

Technical issues

The most frequent problems with Duodopa relate to technical aspects of the therapy such as dislocation of the small intestinal catheter, which occurs in 3-4 % of patients. Displacement of the catheter into the stomach leads to a reappearance of the fluctuating effects of the medication. In such cases the catheter position must be corrected under radiographic or gastroscopic control.

The catheter may also become blocked or kinked. Blockage can usually be eliminated by flushing the catheter with tap water, but kinks may need to be eliminated by repositioning the catheter.

In rare cases the PEG or the catheter can become disconnected from the coupling and may be detached in the stomach or small intestine. If the inner catheter becomes loose it normally exits with defecation without any problem and can simply be renewed. A broken PEG entails a risk of complications, such as perforation of the stomach or intestine, which can necessitate open surgery.

The stoma usually heals without significant complications. However, there may be abdominal pain, infection and discharge of gastric juice shortly after the operation. In rare cases bacterial peritonitis occurs in connection with the PEG application. The most common chronic local complications are secretion and the formation of hypertrophic granulation tissue. Local infection around the stoma is treated with disinfectant, and antibiotic therapy is rarely necessary. Hypertrophic granulation can be treated with class 3 steroid salve.

Pharmacological side effects

The side effects of Duodopa are the same as those of levodopa/carbidopa tablets. Motor fluctuations are less frequent than with tablet therapy.

Some patients report long-term sedation due to levodopa and carbidopa. In addition, sudden sleep episodes (the sudden onset of sleep without prior tiredness or warning signals) can occur as in other PD treatment. Patients treated with Duodopa should therefore be informed to take care when driving or operating machines.

Long-term safety follow-up studies show no further unexpected side effects (> 10 years).

Efficacy

There is no evidence of the development of tolerance to daytime Duodopa therapy. On the contrary, the dose can be reduced in many patients after the first few weeks or months. The situation is less clear-cut with 24-hour therapy, as there have been sporadic reports of the possible development of tolerance that was reversible when 16-hour therapy was resumed. Most patients undergoing 24-hour therapy do not, however, show any signs of tolerance.

References

Antonini A. Continuous dopaminergic stimulation - From theory to clinical practice. *Parkinsonism Relat Disord.* 2007 Sep;13 Suppl:S24-8

Antonini A, Isaias IU, Canesi M, Zibetti M, Mancini F, Manfredi L, Dal Fante M, Lopiano L, Pezzoli G. Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. *Mov Disord.* 2007 Jun 15;22(8):1145-9.

Evidence Level: III

Eggert K., Schrader C., Hahn M., Stamelou M., Rüssmann A., Dengler R., Oertel W., Odin P. Continuous jejunal levodopa infusion in patients with advanced Parkinson's disease: Practical aspects and outcome of motor and non-motor complications. *Clinical Neuropharmacology* 2008; in press

Evidence Level: III

Kurlan R, Rubin AJ, Miller C, Rivera-Calimlim L, Clarke A, Shoulson I. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. *Ann Neurol* 1986;20:262-5.

Evidence Level: III

Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with "on-off" fluctuations. *Neurology* 1993;43:1698-1703.

Evidence Level: Ib

Nilsson D, Hansson LE, Johansson K, Nystrom C, Paalzow L, Aquilonius SM. Long-term intraduodenal infusion of a water based levodopa-carbidopa dispersion in very advanced Parkinson's disease. *Acta Neurol Scand* 1998; 97:175-183

Evidence Level: III

Nilsson D, Nyholm D, Aquilonius SM. Duodenal levodopa infusion in Parkinson's disease--long-term experience. *Acta Neurol Scand* 2001;104:343-8.

Evidence Level: III

Nyholm D, Aquilonius SM. Levodopa infusion therapy in Parkinson disease: state of the art in 2004. *Clin Neuropharmacol* 2004;27:245-56.

Nyholm D, Askmark H, Gomes-Trolin C, Knutson T, Lennernas H, Nystrom C, Aquilonius SM. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. *Clin Neuropharmacol.* 2003 May-Jun;26(3):156-63.

Evidence Level: III

Nyholm D, Lewander T, Johansson A, LeWitt PA, Lundqvist C, Aquilonius SM. Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term exposure. *Clin Neuropharmacol* 2008; in press.

Evidence Level: III

Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson's disease. *Neurology*. 2005;64:216-23.

Evidence Level: Ib

Quinn N, Marsden CD, Parkes JD. Complicated response fluctuations in Parkinson's disease: response to intravenous infusion of levodopa. *Lancet*. 1982;2:412-5.

Evidence Level: III

Samanta J, Hauser RA. Duodenal levodopa infusion for the treatment of Parkinson's disease. *Expert Opin Pharmacother*. 2007 Apr;8(5):657-64.

Shoulson I, Glaubiger GA, Chase TN. On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. *Neurology* 1975;25:1144-8.

Evidence Level: III

Stocchi F, Vacca L, Ruggieri S, Olanow CW. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. *Arch Neurol* 2005; 62: 905-910

Evidence Level: III

Syed N, Murphy J, Zimmerman T Jr, Mark MH, Sage JI. Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. *Mov Disord* 1998;13:336-8.

Evidence Level: III