

## Treatment with Duodopa in patients with Parkinson's disease

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Patients with Parkinson's disease (PD) in advanced stage of the disease should be referred to a Movement Disorders Clinic where a comprehensive and unbiased evaluation can be made by a neurologist specialized in movement disorders with a vast experience of adjusting peroral medication and in the use of deep brain stimulation (DBS), continuous subcutaneous administration of apomorphine and continuous intestinal administration of levodopa.

#### Background

Levodopa-treatment in combination with a dopamine agonist is the golden standard of treatment in PD. As the disease progresses oral medication only to a certain degree can control symptoms and upcoming fluctuations and dyskinesias will dominate. Continuous dopaminergic stimulation is now thought to be a basic principle in the optimal treatment of these problems.

The development of a carboxymethyl-cellulose gel with levodopa/carbidopa (Duodopa®, Solvay Pharmaceuticals GmbH, Hannover, Germany) in the 1990'ies in Uppsala made intraduodenal infusion of levodopa/carbidopa possible. The concentration of levodopa is 20 mg/ml, with a cassette containing 100 ml which is a sufficient daily total 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, where the end of the tube is placed in Duodenum (behind the pylorus) at Treitz ligament. In this position administration of Duodopa is given continuously allowing immediate absorption of the medication across the intestinal mucosa in the duodenum or proximal jejunum. The clinical response of this type of levodopa administration can be tested before establishing a PEG, by temporary Duodopa treatment through a naso-jejunal tube allowing clinicians to evaluate the degree of response and possible side effects.

#### General indications

- Treatment of levodopa-responsive PD in the advanced and complicated phase, with motor fluctuations, "off"-periods and/or hyper-/dyskinesias despite optimized oral/patch/injection treatment
- A condition with sufficiently severe symptoms to necessitate initiation of advanced treatment.

#### Special conditions that may be successfully treated

- When treatment of advanced symptoms by means of DBS is contraindicated, ineffective or otherwise unsuitable
- When treatment of advanced symptoms by means of continuous subcutaneous infusion with dopaminagonists as Apomorphine 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 hours.
- Patients with mild to moderate Parkinson dementia if support from a spouse or

### **Secondary prerequisites that must be taken into consideration when evaluating the patient for treatment.**

- The patients level of independence and general condition
- The patient's social situation, relation to spouses and other relatives and general living conditions
- Care-giver assistance to cognitive impaired patients may be required in the 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 checkups is necessary for successful treatment. A dedicated experienced Parkinson team at a university hospital or Movement Disorder Clinic should be involved in initiating and follow up of treatment. Ideally, specialized units and PD nurses should be available for training, consultation and general education of patients and caregivers.

Each patient should have a tailor-made "optimal" peroral treatment schedule in case of interruptions in the Duodopa due to problems with the pump or tube.

### **Contraindications**

- Hypersensitivity to levodopa or carbidopa
- Narrow angle glaucoma
- Serious liver and kidney disease
- Severe heart failure
- Acute myocardial infarction
- Severe cardiac arrhythmias
- Recent or acute stroke
- Contraindications for adrenergic effects; pheochromocytoma, hyperthyroidism, Cushing's syndrome
- Other contraindications for abdominal surgery.

### **Relative contraindications**

- Significant dementia, which makes the treatment more difficult to perform and leads to less favorable outcomes
- Patients with non-compliance or no care-giver support
- Patients with levodopa resistant Parkinsonism
- Ongoing treatment with unselective MAO inhibitors or selective MAO-A inhibitors (to be withdrawn at least two weeks before the start of treatment)
- Therapy resistant psychosis due to dopaminergic medication
- Polyneuropathy.

### **Pre-treatment period**

After considering a patient for intraduodenal levodopa treatment, the patient and also the spouse must be adequately informed about the treatment and the expected results of treatment. The patient must also be given information about the surgical procedures of the PEG operation. Information about long-term experiences with Duodopa® and the circumstance of living with a pump and the complications must be shared. There must be an agreement with informed consent to treatment. The patient must be given a schedule of the procedures during the stay in the neurological department. Selected blood samples must be taken in advance. Neurophysiology should be considered in risk-patients concerning polyneuropathy.

The temporary naso-jejunal tube is applied. The initial dosage of the levodopa/carbidopa gel is calculated on the basis of the previous dose of oral levodopa or levodopa equivalents. Both morning dose and infusion rate are titrated and 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. The infusion rate can be adjusted in small increments of 0.2 ml/h.

After titrating an individual morning bolus, usually 1-10 ml levodopa/carbidopa gel is used to rapidly achieve steady-state, after which the concentration can be kept constant by the individualized infusion rate. The continuous daily dose is normally between 20-120 ml/day levodopa/carbidopa enteral gel. An individually set extra bolus dose on demand is possible (normally, 10-40 mg). After a few days of treatment, the clinical effect and possible side effects of Duodopa® is evident. If indication the permanent PEG-tube can then be established.

Normally, the total length of admission for Duodopa pump start is 1.5 weeks.

Normally, the patient is discharged from the hospital a few days after the PEG surgery, where an optimal dose found, and the patient or a relative or a caregiver has learned how to operate the infusion system. The titration period can continue at home using telemedicine. Follow-up should be carried out by a PD nurse or at an outpatient clinic visit a few weeks later, but more frequent visits may be needed. The dosage may need to be adapted after some weeks to months, probably due to long-term plasticity changes in the brain. The levodopa/carbidopa infusion has mostly been used as monotherapy, but can, if necessary, be combined with other anti-parkinsonian drugs, especially for treatment of non-dopaminergic symptoms. Initially the treatment is only administered during the day, and a long-acting levodopa preparation and/or peroral/patch dopamine agonist is given at bedtime.

### **Special circumstances**

Continuous administration of the liquid levodopa/carbidopa smoothed plasma concentrations, which probably accounts for the clinical effect. Improvements can be seen in dyskinesias and dopaminergic side effects in spite of an unchanged or even increased total daily levodopa dose. Psychotic side effects due to dopaminergic stimulation may improve on infusion with levodopa/carbidopa. Also other non-motor symptoms such as sleep/fatigue, pain gastrointestinal and urinary problems together with sexual dysfunction can improve after switching to pump therapy. Studies have now shown, that Duodopa® is superior compared til Apomorphine pump and conventional peroral therapy in this respect.

Duodenal Levodopa Infusion for Long-term Deep Brain Stimulation-refractory Symptoms as axial symptoms can be used in advanced PD.

**Pharmacological side effects** The adverse events of infusion with levodopa/carbidopa gel is the same as in oral medication, and should be handled in accordance to the same principles, as when dealing with oral treatment adverse events. Psychosis is treated in the same manner as in oral medication with at pause in infusion.

Polyneuropathy, sometimes severe, has been reported in patients on Duodopa. It is still unclear if this relates to the Duodopa treatment, to L-dopa treatment in general or to the disease process. These reported cases are generally of type sensorimotor polyneuropathy with both subacute and chronic onsets, often associated with vitamin B12 deficiency. They have often responded to vitamin supplementation, often without need for Duodopa cessation. It is advisable to monitor vitamin B6/B12/Folic acid status, by analysing S-Homocystein, before and after patients start LCIG (after 1, 3 and 6 months and thereafter annually). It is also important to be vigilant for signs of polyneuropathy. Another alternative is to substitute both vitamine B6, B12 and folic acid as a routine but S-Homocystein must be monitored as above.

Some patients experience weight loss due to levodopa treatment. It is therefore important to monitor the weight at each clinical control and if weight loss contact a dietician for prescription of energy subsidies.

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

### **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. These problems are now less prominent than in the beginning of the treatment with Duodopa 10-15 years ago because of technical improvements. Displacement of the catheter into the stomach, leads to a reappearance of the fluctuating symptoms and a decline in the efficacy of the medication. In such cases the catheter position must be corrected under radiographic control.

The catheter may also become blocked or kinked. Blockage can usually be eliminated by flushing the catheter with tap water, or introduction of the guide wire. 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 disconnected it normally exits with defecation without any problem. A broken PEG entails a risk of complications, such as perforation of the stomach or intestine, which can necessitate open surgery. In such a case a gastroenterologist must be consulted.

If persistent abdominal pain, a gastroscopy should be performed. If signs of gastrointestinal infection, antibiotics should be given according to the clinical condition and local guidelines.

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 (in 1% of patients). 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 1-3 steroid ointment.

Technical problems may often require immediate contact by telephone or visit to an outpatient clinic to be solved. Patients must therefore be able to have access to an immediate contact to a PD nurse or department.

### **Efficacy variables from treatment**

- When responding to the levodopa/carbidopa treatment motor symptoms, fluctuations and dyskinesias are alleviated to a large degree
- Non-motor symptoms are often effectively treated and becomes less prominent
- Quality of life and quality of sleep have shown to be improved
- Levodopa/carbidopa treatment can be administered with equal beneficial efficacy for a variable time range up to 24 hours. 24-hours treatment may require different dosages during daytime and at nights (normally 2/3 of the daytime dose at nights).

There is no evidence of the development of tolerance to daytime levodopa/carbidopa gel 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

tolerance.

Long term experience with Duodopa® treatment is good with an unchanged efficacy and tolerability to treatment. A typical length of treatment is 8 years, and for many patients this becomes a life-long therapy.

### **Assessment**

It is recommended that patient's who are suitable to Duodopa® treatment is followed according to an established local protocol using rating scales and video's for measuring and documenting the effect and outcome of treatment.

### **End of treatment**

In the case where the patient develops severe dementia or advanced malignancy or other serious medical conditions, where the patient is not benefiting from treatment, has no active motor ability and perhaps no ability to communicate, termination of Duodopa treatment should be considered. Ethical aspects in decision making must be taken into consideration. Patients should after termination of treatment, be offered optimal standard oral treatment, palliative care and regular consultations.

### **Socioeconomics**

Duodopa® treatment is rather expensive, so the total cost for society as well as the benefit for the patient must be taken into consideration, when evaluating a patient for the treatment.

Factors that can contribute to make the therapy cost-effective:

- Significant improvement in motor ability with reductions in fluctuations and hyperkinesias
- Independence of gait and mobility
- Significant benefit in non-motor symptoms
- Significant increase in patient autonomy and independency measurable with standard ADL scores
- Care-giver burden will be reduced, since independency in patients will improve
- Aspects of quality of life for the patient as for the spouses/relatives must be considered as an operational measure for treatment
- Nursing costs for the care of the patient will be reduced. Need for nursing homes reduced
- The reduction in total costs due to withdrawal of the oral medication must be in calculated
- Different possible therapy strategies must be considered.

### **Name of the product**

Duodopa® (levodopa/carbidopa enteral gel, 20mg/ml+5 mg/ml).

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