Long-term Efficacy and Safety with Continuous Dopaminergic Stimulation Pump Treatments in Parkinson's Disease

Karin Busk,[1] Anders Johansson[2] and Dag Nyholm[3]

1. Biomedical Student; 2. Post-doctoral Researcher and Consultant Physician;
3. Associate Professor, Department of Neuroscience, Neurology, Uppsala University

Abstract

Continuous dopaminergic stimulation (CDS) is important for symptom control in advanced stages of Parkinson's disease (PD). The most efficacious approaches are pump treatments with dopaminergic drugs: subcutaneous infusion of the dopamine receptor agonist apomorphine and intestinal infusion of levodopa/carbidopa gel. Both methods decrease motor fluctuations in long-term follow-ups, including parkinsonian and dyskinetic states, when compared to conventional optimised oral therapy. Also non-motor symptoms may be improved. Adverse drug reactions are usually less pronounced although high levodopa doses, which are common with levodopa/carbidopa infusion, may cause hyperhomocysteinaemia and cobalamin deficiency. Technical complications are specific for each infusion strategy. Formation of subcutaneous nodules is the most common problem with apomorphine infusion. Dislocation of the intestinal tube is the most common problem with levodopa/carbidopa infusion. Both pump treatments may be used for 24-hour infusion in selected patients. The long-term experience is reviewed. To conclude, CDS pump treatments may be successfully used for several years in advanced PD.

Keywords

Apomorphine, continuous dopaminergic stimulation, infusion, levodopa/carbidopa, Parkinson's disease, pump

Disclosure: A postdoctoral grant from Uppsala University was used. No other funding was available for this work. Karin Busk has no conflicts of interest to declare. Anders Johansson has received speaker fees from Abbott Products. Dag Nyholm serves as a consultant to Abbott Products and has received speaker fees from Nordic InfuCare.
Received: 2 May 2011 **Accepted:** 10 August 2011 **Citation:** *European Neurological Review*, 2011;6(3):156–60 *DOI:10.17925/ENR.2011.06.03.156*
Correspondence: Dag Nyholm, Department of Neuroscience, Neurology, Uppsala University, Uppsala, SE-75185, Sweden. E: dag.nyholm@neuro.uu.se

The continuous dopaminergic stimulation (CDS) concept dominates the current therapeutic management of Parkinson's disease (PD), especially in moderate to advanced stages of the disease. The background is a combination of a number of findings, mainly that:

- striatal dopaminergic stimulation is fairly constant in a healthy brain;
- striatal dopaminergic stimulation in PD is pulsatile when oral levodopa is used;
- pulsatile dopaminergic stimulation causes motor fluctuations and dyskinesias; and
- continuous administration of dopaminergic agents may decrease motor fluctuations and reverse dyskinesias.

PD is associated with a more widespread pathology than nigro-striatal degeneration and CDS is not the remedy for all problems. But there is firm evidence that continuous dopaminergic drug delivery, probably providing CDS, produces a significant benefit compared to conventional therapy in patients with advanced PD. The evidence mainly stems from studies of levodopa and apomorphine infusions.

Background

Strategies that provide more or less continuous dopaminergic stimulation have evolved in all stages of PD during the last decade. For orally administered levodopa, fractionation of dosage is the main CDS-like strategy. Available sustained-release formulations have been disappointing regarding pharmacokinetics and addition of catechol-O-methyltransferase inhibitors cannot provide stable levodopa concentrations either.[1–3] Long-acting dopamine agonists and Monoamine oxidase (MAO-B) inhibitors have been developed in line with the CDS concept but are usually not efficacious enough to completely replace levodopa in moderate to advanced stages of PD.

Stable pharmacokinetics of substances efficacious enough to be used as monotherapy in advanced PD is only achieved by means of pump treatments. The two most widely used pump alternatives are reviewed in this paper: subcutaneous apomorphine (APO) and levodopa/carbidopa intestinal gel (LCIG).[4,5] Relevant literature on long-term use was found using the Pubmed database. Previous long-term studies with water solutions of levodopa were not included in the review because there is no such marketed alternative available.[6,7] Levodopa esters and lisuride have been used in some countries but are not reviewed due to limited experience.[8,9]

Deep brain stimulation (DBS) is another alternative for advanced PD.[10] The continuous electrical stimulation can be regarded as an analogue to CDS. So far, there are no randomised comparative studies of APO, LCIG and DBS and patient selection is partly overlapping. Patients <70 years of age with young onset, excellent levodopa response, severe fluctuations and/or dyskinesias and relatively intact cognitive functions are good candidates for all three alternatives. Due to more strict contraindications for DBS,[11] patients with high age or co-existing

Table 1: Long-term, Open-label Efficacy Studies of Subcutaneous Apomorphine

Study	Number of Patients	Age (Years)	PD Duration (Years)	Duration of Follow-up	Main Outcome Regarding Symptoms, Compared to Conventional Therapy	Mean Improvement in Off Time (%)
Stibe et al., 1988[15]	11	32–70	9–20	1–15 months	Off↓	62
Frankel et al., 1990[16]	25	40–74	7–24	5–32 months	Off↓	55
Hughes et al., 1993[17]	22	43–75	9–28	12–61 months	Off↓	59
Poewe et al., 1993[18]	18	49–72	4–24	8–35 months	Off↓	58
Stocchi et al., 1993[19]	10	60±8.6	11.5±5.3	6–24 months	Off↓	58
Colzi et al., 1998[20]	19	47–70	12–31	9–108 months	Off↓, dyskinesia↓	72
Pietz et al., 1998[21]	25	64.7±6.8	6–27	3–67 months	Off↓	50
Wenning et al., 1999[22]	16	60	11	8–103 months	Off↓	55
Stocchi et al., 2001[23]	30	62±8.5	14.8±5.5	60 months	Dyskinesia↓	NA
Kanovsky et al., 2002[24]	12	64.3±9.2	14.4±6.3	24 months	Dyskinesia↓	80
Manson et al., 2002[25]	45	44–76	16.2±7.3	4–108 months	Off↓, dyskinesia↓	50
Alegret et al., 2004[26]	7	51–71	11–17	12 months	Off↓	53
Morgante et al., 2004[27]	12	54±9	10±3	24 months	Off↓, mood↑	38
Tyne et al., 2004[28]	80	~61	2–29	Up to 84 months	Off↓	51
Katzenschlager et al., 2005[29]	12	51–80	6–23	6 months	Off↓, dyskinesia↓	38
De Gaspari et al., 2006[30]	13	59±13	10±5	12 months	Off↓	51
Garcia Ruiz et al., 2008[31]	82	67±11	14.4±5.7	20±16 months	Off↓, dyskinesia↓	80
Antonini et al., 2011[32]	12	58±12	~9	Up to 60 months	Off↓	49

NA = Not available; PD = Parkinson's disease.

psychopathology are selected for pump treatments instead. Accordingly, some infusion studies have included patients in very advanced disease stages.[12,13]

Evidence Level of Pump Treatments

Long-term experience with both APO and LCIG infusions has grown considerably during the last decade. Evidence levels regarding efficacy are good for both but higher for LCIG due to two short-term randomised controlled trials. LCIG is therefore considered to have Level 1 evidence and APO Level 2.[14] All long-term studies have been open-label. Safety issues are almost exclusively related to the infusion systems and not to the drugs. It is likely that CDS therapies not only stabilise motor and non-motor symptoms but also decrease side-effects. However, important problems associated with advancing PD, such as cognitive decline and disequilibrium, may not be successfully treated by any dopaminergic therapy but often dominate the clinical picture. Both pump methods are intended for small populations of severely affected patients and double-blind, placebo-controlled trials are difficult to employ. Therefore, there is a lack of well-designed long-term studies so far, but new results are in progress.

Long-term Efficacy with Apomorphine Infusion

A summary of long-term efficacy studies of APO is presented in *Table 1*.[15–32] The general finding is that APO provides more time in motor states near normal performance and less time in 'off' and dyskinetic states as compared to conventional optimised therapy. Improvement in quality of life (QoL) may accompany the increased 'on' time, but so far publications on this aspect of APO infusion are sparse.[33,34] Oral levodopa dosage may often be substantially reduced, and monotherapy with APO is possible in some cases.[25] Monotherapy was as effective as polytherapy regarding reduction in 'off' time, but more effective in decreasing dyskinesias.[25] A possible reason for this finding is that high peak concentrations of levodopa are avoided or that sensitisation is partly reversed with continuous drug delivery.[29]

Long-term Efficacy with Levodopa/Carbidopa Intestinal Gel Infusion

A summary of long-term efficacy studies of LCIG is presented in *Table 2*.[12,13,35–46] Most studies so far have focused on motor symptoms. The general finding is that LCIG provides more time in motor states near normal performance and less time in 'off' and dyskinetic states as compared to conventional optimised therapy.

Table 2: Long-term, Open-label Efficacy Studies of Levodopa/Carbidopa Intestinal Gel

Study	Number of Patients	Age (Years)	PD Duration (Years)	Duration of Follow-up	Main Outcome Regarding Symptoms, Compared to Conventional Therapy	Mean Improvement in Off Time (%)
Nilsson et al., 1998[35]	9	47–69	10–26	6–30 months	Fluctuations↓	43 (n=2), 29 (n=7)
Nilsson et al., 2001[13]	6	45–83	6–26	4–7 years	Fluctuations↓	–28 (n=6), 28 (n=5)*
Nyholm et al., 2005[36]	5	47–64	9–26	13–37 months	Fluctuations↓	NA
Antonini et al., 2007[37]	7	50–80	12–28	12 months	Off↓, dyskinesia↓, QoL↑	87
Antonini et al., 2008[38]	22	NA	NA	Up to 24 months	Off↓, dyskinesia↓, QoL↑	46
Eggert et al., 2008[39]	13	44–71	10–26	12 months	Off↓, dyskinesia↓, anxiety↓, sleep↑	70
Nyholm et al., 2008[40]	65	39–79	6–30	Up to 10.7 years	Fluctuations↓	NA
Honig et al., 2009[41]	22	59±9	12–17	6 months	Non-motor↓, sleep↑, QoL↑	NA
Raudino et al., 2009[42]	6	56–77	10–20	10–35 months	Off↓	31
Devos et al., 2009[12]	75	73±11	17±6	4 years	Fluctuations↓, QoL↑, autonomy↑	NA
Antonini et al., 2010[43]	19	NA	NA	Up to 36 months	Off↓, dyskinesia↓	NA
Karlsborg et al., 2010[44]	12	65±14	16.2±7.4	2–43 months	Off↓, dyskinesia↓	NA
Puente et al., 2010[45]	9	57–76	9–23	18 months	Off↓, QoL↑	67
Merola et al., 2011[46]	20	57–79	8–27	7–30 months	Off↓	~40

NA = Not available; PD = Parkinson's disease; QoL = quality of life, according to 8-item or 39-item PD Questionnaire.
**The groups (n=6) was worsened in off time after four to seven years due to one patient with gait difficulties, therefore improved off time for the remaining five patients was reported separately.*

Most studies are open-label due to the major difficulties in performing a true double-blind study with LCIG. Blinded evaluations are available in one short-term study of LCIG as monotherapy,[47] where patients were significantly improved in UPDRS scores and 'on' time. Patients did not have much moderate/severe dyskinesias during conventional therapy, so no difference was demonstrated. Improvement in QoL accompanies the increased 'on' time.[37,48] Non-motor symptoms are likely to significantly affect QoL and several such symptoms were improved by LCIG in a six-month study.[41] Cognitive function was reported to be improved in two patients, two to 24 months after the introduction of LCIG, possibly related to increased 'on' time.[49] In an interview with 25 patients, of whom the majority had been using infusion for more than two years, 76 % agreed completely that their QoL was improved with infusion as compared to before. Twenty-four percent agreed in part and no one disagreed to the statement. All but one (96 %) recommended the treatment to someone else.[50]

Safety with Long-term Pump Treatments

Both APO and LCIG can cause typical dopaminergic side-effects such as nausea, loss of appetite and dyskinesias. Some patients report long-term sedation with dopaminergic therapy. Sudden onset of sleep without prior tiredness or warning signals can occur in relation to the treatment, as is the case with other PD treatments. Patients with pump treatments should therefore be informed to take care when driving or using machines. Driving ability is impaired in advanced PD, irrespective of treatment.

Safety with Apomorphine Infusion

Safety issues regarding APO can be divided into adverse drug reactions and technical complications with pump or needles. The most common side-effect is the formation of subcutaneous nodules which can interfere with absorption of APO.[51] Ultrasound may be used for local treatment of nodules.[52] Haemolytic anaemia is a specific but uncommon adverse drug reaction. Dopamine agonists are generally considered to cause more hallucinations than levodopa. In a six-week open-label study of eight patients with visual hallucinations, a significant reduction in severity of hallucinations was demonstrated after initiation of APO.[53] Levodopa equivalent doses and cognitive performance were unchanged. The authors speculated that discontinuation of oral dopamine agonists was the explanation for the improvement of hallucinations and that apomorphine might have beneficial properties regarding visual processing.[53,54]

Safety with Levodopa/Carbidopa Intestinal Gel Infusion

Safety issues regarding LCIG can be divided into adverse drug reactions, adverse events in relation to percutaneous endoscopic gastrojejunostomy (PEG-J) surgery, and technical complications with pump or tubing. The side-effects of levodopa/carbidopa are well-known and most patients have experienced dyskinesias and hallucinations before initiation of LCIG. Depression is common in advanced PD. Although a case of suicide has been reported, there is no evidence of impaired mood with LCIG.[55] Recently, a number of reports have suggested a possible relationship between LCIG,

hyperhomocysteinaemia and polyneuropathy. A few cases of acute inflammatory demyelinating polyneuropathy have been reported, one associated with encephalopathy.[56] The causality is so far not established because neuropathy may be very common in PD patients[57] and there is no clear relationship between levodopa and neuropathy.[58] However, it is well-known that levodopa is involved in the metabolism of vitamin B12 and causes hyperhomocysteinaemia. High levodopa/carbidopa doses are often used with LCIG because it is used as monotherapy. Cumulative levodopa dose and elevated methyl malonic acid have been suggested to be correlated with severity of neuropathy.[59] Decreased vitamin B6 levels were found in two patients on LCIG and neuropathy.[60]

The most common problem with LCIG is dislocation of the intestinal tube.[40] Due to displacement of the tip of the tube back into the stomach, fluctuating effects of medication reappear. The catheter position then has to be corrected under radiographic or gastroscopic control. In rare cases the PEG or the catheter detaches or breaks in the stomach or the small intestine. If the catheter gets loose it normally passes the gastrointestinal tract without further problems and can simply be renewed. However, a broken PEG is a risk for serious complications, like perforation of the stomach or intestine, and may necessitate open surgery. The tube may also become blocked, kinked or even form knots inside the small intestine.[61] Two cases of tube problems have been reported after consumption of asparagus.[62] The fibres of asparagus had formed a phytobezoar around the tip of the tube. The stoma usually heals properly. However, there may be abdominal pain, infection and leakage of gastric juice shortly after the operation. In rare cases, bacterial peritonitis have occurred in connection with the PEG application. The most common chronic local complications are secretion and the formation of hypertrophic granulation tissue. Local infections around the stoma are treated with disinfectants. Antibiotic therapy is rarely necessary.

An alternative to PEG-J tubes is the transcutaneous titanium port (T-port), which has been used in two research studies.[63,64] The T-port is inserted as a radiological gastrostomy, without need of endoscopy.

Long-term Experience of 24-hour Apomorphine Infusion

Around-the-clock infusion of APO is primarily used in patients with disabling motor fluctuations in spite of optimal oral treatment and apomorphine injections, especially if severe night-time symptoms are present. The long-term effect of 24-hour APO infusion appears to be constant. In a 21-month prospective study of 18 patients receiving around the clock APO off periods were reduced by 60 % during the entire follow-up period.[18] A comparative study of treatment around the clock and daytime-only was not able to show a difference in reduction of daily off time between the groups.[22] Another comparative study showed that patients with 24-hour infusions often had improved quality of the on and off phases.[21] Patients treated around the clock on average receive a twofold higher daily dose than those on daytime-only infusions. The dosage remained stable in both groups during the follow-up period, indicating that there was no development of tolerance.[22]

Around-the-clock infusions of APO have been associated with increased psychiatric side effects such as nightmares, confusions, hallucinations, and psychosis. A study of 49 patients followed for 54 months showed that psychiatric side effects occurred in 44 % of the around-the-clock treated patients and only in 12 % of those treated daytime-only. The higher percentage in the 24-hour treated group could be explained by the higher daily doses they receive. Most could be controlled by reduction of antiparkinson treatment or antipsychotic drugs, but 10 % had to terminate treatment due to psychiatric side effects.[21] Preferably, patients should be cognitively well preserved and without severe psychiatric side effects on other antiparkinson drugs before initiating 24-hour infusions of APO.

Long-term Experience of 24-hour Levodopa/Carbidopa Intestinal Gel Infusion

Nocturnal and early-morning off symptoms causing sleep disturbance and affecting quality of life is the primary reason to initiate 24-hour LCIG treatment. Around-the-clock infusion is not a generally recommended treatment due to fear of developing tolerance and psychiatric side effects, such as hallucinations and paranoia. Around-the-clock infusion can substitute oral nocturnal intake of LD providing more continuous sleep pattern. Increased motor performance and quality of sleep have been observed in patients with long-term 24-hour LCIG infusions.[36] In a six-month prospective LCIG study five patients suffering from marked nocturnal off symptoms associated with pain and sleep disturbances substantially improved in nocturnal and early morning akinesias after initiating 24-hour LCIG infusion, providing better quality of sleep.[39]

A report of one patient treated with 24-hour levodopa infusion showed a need of a rapidly increased infusion rate, 16 % in five weeks, due to continuous decrease in motor function indicating development of tolerance.[65] The tolerance was reversed when the patient went back to daytime-only infusion. In a prospective study of 14 patients out of which three patients received 24-hour treatment the mean consumption of LD was increased by 9.3 % in the around the clock patients compared to a 1.6 % increase in the daytime treated patients. The efficacy did not decrease in any of the groups, indicating that there was no development of tolerance despite the increased total dosage in the 24-hour group.[44]

Continuous infusion of LCIG around the clock is poorly documented. The studies conducted had few patients and are performed under short periods of time and there is a need of larger long-term studies within the field.

Head-to-head Comparisons

There are no prospective comparative studies between LCIG and APO. Both methods are very potent and maximal effects of the two therapies regarding motor symptoms are probably of similar degree. There is more recent work on LCIG in the literature (see *Tables 1* and *2*). Therefore, effects on aspects of PD that have received more focus in recent years, such as non-motor symptoms and QoL, are better documented for LCIG. It seems that more patients can be treated with monotherapy LCIG compared to monotherapy APO. This could indicate that the effect of levodopa infusion is stronger or more complete. A report on four cases suggested that LCIG was more effective than APO, but the cases were included in a study of LCIG, thus were not content with their ongoing APO therapy.[66]

Technical–practical aspects and side effects differ between the methods. With LCIG, a surgical intervention is necessary, with APO not. With APO infusion, local skin irritation (nodule formation) is

frequent, with LCIG not. In patients on APO therapy who develop numerous skin reactions, a change to LCIG therapy can be considered. Compared to DBS, APO infusion similarly decreases 'off' time, but not dyskinesias, according to two one-year studies[26,30] and a five-year prospective study.[32] A similar result was seen in a retrospective analysis of LCIG and DBS, but the DBS group was examined stimulation-on/medication-off, which could explain the difference in dyskinesias.[46] Both pump methods are more expensive than conventional methods. Modelling of cost–benefit is of great interest in discussions of reimbursement.[67]

Conclusions

Treatment with pumps provide stable drug concentrations and reduced motor fluctuations and dyskinesias compared to treatment with conventional therapy. Although technical complications occur with both pump methods, these are usually not severe. ■

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