Continuous Dopaminergic Stimulation in Focus

Update on Levodopa/Carbidopa Intestinal Gel Infusion

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Abstract
Recent data on levodopa/carbidopa intestinal gel (LCIG) infusion are discussed in this article. LCIG infusion provides improvements in ‘off’ time and dyskinesias via continuous dopaminergic stimulation (CDS). In the long-term, LCIG infusion appears to maintain efficacy without the need to increase dosages. The growing number of publications on LCIG infusion shows the increasing experience and interest in this therapy. The new data demonstrate the effects of using LCIG infusion in combination with catechol-O-methyl transferase inhibitors, and technical improvements to the pump system (e.g., to the tubing). Despite the invasive nature of LCIG infusion, nearly all patients would recommend this treatment. Furthermore, a number of larger-scale studies on this particular CDS therapy are in progress.

Keywords
Parkinson’s disease, levodopa, continuous dopaminergic stimulation, levodopa/carbidopa intestinal gel, motor fluctuations

Disclosure: Dag Nyholm serves as a consultant to Abbott, who sponsored research in which he served as principal investigator. He also serves as a consultant to AstraZeneca and Serono/Allergan; has received consultancy fees from Shire, Biocon; has received research support from Abbott and Kibion AB; is a co-founder and a shareholder in Jena Med A/S; has served on the advisory boards of AstraZeneca, Serono-Allergan, Neuroscience at Scale Ltd, and NeuroActa; and receives remuneration from the website netdoktor.se for participation in an expert panel.

Acknowledgements: The V International Forum on Parkinson’s Disease (Helsinki, Finland, 6–7 May 2011) was funded by an unrestricted educational grant from Abbott. Dag Nyholm participated in an expert panel.

Received: 22 June 2012 Accepted: 6 August 2012 Citation: European Neurological Review, 2012;7(Suppl. 1):13–6

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In 1975, it was shown that achieving stable plasma levodopa levels by continuous intravenous infusion of levodopa rapidly stabilised motor fluctuations in Parkinson’s disease (PD) patients.1 However, intravenous levodopa infusion did not become a practical treatment option in PD because of the technical complexity of administration.2 In the mid-1980s, it was shown that enteral (duodenal/jejunal) infusion of levodopa achieved stable plasma levodopa concentrations and reduced motor fluctuations,3 but the large volumes of levodopa/carbidopa solutions involved were cumbersome and impractical. It was only when a gel formulation of levodopa/carbidopa was developed that enteral infusion became a viable therapy. This levodopa/carbidopa intestinal gel (LCIG) infusion therapy has undergone further development and testing in patients.4 The recent data on this therapy, collected until May 2011, are discussed in this article.

Recent Findings on Levodopa/Carbidopa Intestinal Gel Infusion Pharmacokinetics and Pharmacodynamics

Several recent studies have examined the pharmacokinetics and pharmacodynamics of LCIG infusion treatment. One of these studies aimed to identify and estimate characteristic parameters of a population pharmacokinetic-pharmacodynamic model for LCIG infusion, in order to better understand the pharmacological properties of this levodopa formulation.5 A model was developed based on pooled data from three studies in patients with advanced Parkinson’s disease (APD).

The study showed that absorption of LCIG can be adequately described with first-order absorption (mean absorption time of 28.5 minutes) with a bioavailability of 88 % and a lag time of 2.9 minutes. The parameters were relatively well determined, with standard errors of 4–43 %. The best pharmacodynamic model was of the effect compartment sigmoid E_{max} type with a steep sigmoidicity coefficient (Hill=11.6), a half-life of effect delay of 21 minutes, a concentration at 50 % effect of 1.55 mg/l, and an E_{max} of 2.39 units on the treatment response scale. This model may be a first step towards model-guided treatment individualisation of LCIG infusion.

A second, observational study assessed the pharmacokinetics of LCIG infusion therapy and the effects on motor symptoms in five patients with difficult-to-treat dyskinesias.6 In this non-randomised, partly blinded, investigator-initiated trial, LCIG doses of 80–120 % of individually and clinically optimised dosage were infused during five 4-hour periods. Plasma samples for levodopa determination, video recording for blinded assessment and objective movement analysis were performed every 20 minutes during the first hour of each 4-hour period and every 30 minutes thereafter. In all patients, individual correlations between plasma levodopa concentrations and corresponding motor scores 20–30 minutes after the sampling time were significant (p<0.05) (see Figure 7). Motor scores were generally stable during the 4-hour periods. Scores on the Treatment Response Scale (TRS) were positive even at 80 % of the optimised LCIG dose, which indicates dyskinesia even at this lower-than-optimised dose of LCIG. Measurement of movement time by objective movement analysis showed that the more dyskinetic the patients were, the faster their motor performance. Therefore, motor performance may be improved with moderate dyskinesia versus mild dyskinesia.
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The results suggest that there is no ideal therapeutic window in these patients, but that LCIG infusion leads to stable motor performance.

The long-term pharmacokinetics and efficacy of LCIG infusion have also been investigated in a study involving 19 patients with APD whose motor fluctuations and dyskinesia were not controlled by oral medications. The patients’ oral medications were withdrawn, and they received LCIG infusion for 14 hours per day, plus levodopa boluses in the morning and during ‘off’ periods. The patients were evaluated by the Unified Parkinson’s Disease Rating Scale (UPDRS) in the morning ('on') and 60–120 minutes after the infusion ('off') at baseline and for a mean follow-up of 13.5 ± 12.5 months. In addition, plasma levels of levodopa and its metabolite 3-O-methyl-dopa (3-O-MD) were measured.

Plasma levodopa concentrations correlated with the daily dose of LCIG infusion, and 3-O-MD concentrations correlated with levodopa levels. Furthermore, 3-O-MD:levodopa ratios were stable over the day. It was shown that a decline in UPDRS-III scores correlated with decreasing 3-O-MD:levodopa ratios. LCIG infusion treatment led to a marked improvement in dyskinesia (UPDRS-IV, items 32–34) over time, but this was not related to levodopa levels, 3-O-MD levels or 3-O-MD:levodopa ratios. While it is possible that continuous infusion decreases levodopa metabolism, the results suggest tolerance does not develop even after several months of continuous infusion. There is also evidence that pharmacodynamic factors may be involved in afternoon ‘off’ periods.

Levodopa/Carbidopa Intestinal Gel Infusion in Combination with Catechol-O-methyl Transferase Inhibitors

Catechol-O-methyl transferase (COMT) is an enzyme involved in the metabolism of levodopa to produce 3-O-MD, and COMT inhibitors may be co-administered with levodopa to extend its effect. In clinical practice, however, COMT inhibition (with peroral levodopa) does not provide CDS, as peaks and troughs in plasma levodopa concentrations are still observed. We investigated the possibility of using a COMT inhibitor, such as entacapone or tolcapone, in combination with LCIG infusion in a short-term, randomised, partly blinded pilot study. The objectives were to assess whether the addition of a COMT inhibitor would allow the infusion dose to be reduced by 20 % without motor fluctuations worsening, and to determine the stability of plasma levodopa concentrations.

Ten patients received LCIG (100 % of optimised dose), LCIG (80 % of optimised dose) plus entacapone, or LCIG (80 % of optimised dose) plus tolcapone on different days. The primary outcome measure was the difference in coefficient of variation of plasma levodopa concentrations between the three treatments. Secondary outcome measures included other pharmacokinetic variables, patient-reported outcome and blinded analysis of motor performance.

We found no difference in the variation of plasma levodopa concentrations between the three treatments (see Figure 2). Thus, when co-administered with a COMT inhibitor, a 20 % lower LCIG dose resulted in the same plasma levodopa concentrations as a 100 % LCIG dose. Plasma concentrations of 3-O-MD were constant for LCIG, but decreased gradually with LCIG plus entacapone and LCIG plus tolcapone. Furthermore, motor performance was similar for all three treatments (see Figure 3). The average TRS scores were 0–1, indicating mild dyskinesia that was stable over time.
As LCIG infusion at a dose reduced by 20% plus COMT inhibitor does not significantly affect the stability of plasma levodopa levels or increase ‘off’ time, oral COMT inhibitors administered in 5-hour intervals may be useful in cases where a reduction of LCIG infusion dose is needed. In fact, tolcapone being more potent than entacapone, an even greater reduction of LCIG dose would possibly be required to avoid increased dyskinesias with time.

**Refinement of the Pump System**

In the early years of LCIG infusion (1991–2002), the most common problem was dislocation of the tip of the tube to the stomach. Since 2003, the use of tubes with pigtail-shaped distal ends has considerably reduced the frequency of dislocations, but these tubes can also cause problems. An alternative tubing system, the transcutanous soft-tissue anchored titanium port (T-port), has been developed and evaluated in patients.

In a study conducted in 15 PD patients, the maximum duration of T-port use was 4.9 years, with the main complications being perforation of the skin by the straight flange, local infections resulting from leakage of LCIG, problems with T-fasteners and poor hygiene. Hypergranulation tissue was often reported as a consequence of local inflammation or infection resulting from LCIG leakage, poor hygiene, and/or an overly mobile T-port. The study showed that the most recent version of the T-port (generation III), in combination with more optimised implantation and gastrostomy techniques, led to considerable improvements.

A second study evaluated T-port in 15 patients, seven of whom were LCIG-naïve (non-percutaneous endoscopic gastrojejunostomy [PEG]) and eight of whom had previously received LCIG (former-PEG). At baseline and six-month follow-up, motor scores were assessed by UPDRS-III and quality of life was evaluated by the 8-item Parkinson’s Disease Questionnaire (PDQ-8). At the end of the study, four T-ports had been explanted. There was moderate improvement in UPDRS-III and PDQ-8 scores in the non-PEG patients. In contrast, scores did not change in the former-PEG patients. Two former-PEG patients developed polyneuropathy, but there were no obstructions, retractions or leakages. It was found that most patients preferred the technical and hygienic properties of the T-port.

**Long-term Data**

The long-term data on LCIG infusion therapy are limited. In a recent retrospective study, long-term LCIG infusion was investigated in 135 patients. A retrospective review of medical records was performed to assess the duration of treatment, patient demographics, concomitant medications and reasons for discontinuation of treatment.

The mean age of the patients at diagnosis of PD was 49 years, and the mean age when LCIG infusion therapy was initiated was 63 years. The mean ± standard deviation and median treatment time on infusion were 4.2 ± 3.5 years and 3.4 years (range, 0–16 years), respectively, and the restricted mean treatment time was nearly 8 years. A Kaplan-Meier plot illustrating treatment time on LCIG infusion is shown in Figure 4.

Levodopa (always in combination with a decarboxylase inhibitor) was used as monotherapy in 85 (63%) of the patients at both initiation and last visit (i.e., LCIG alone or in combination with night-time sustained-release levodopa tablets). In addition, LCIG dosage was stable over time. The use of laxatives (p=0.001), antithrombotic agents (p=0.001), vitamin B12 and folic acid (p<0.001) and other urologicals (including antispasmodics [p=0.009], antipsychotics [p<0.001], anxiolytics [p=0.001], antidepressants [p<0.001] and anti-dementia drugs [p=0.006]) was significantly increased between the initiation of LCIG infusion and the last visit.

Thirty-one patients stopped LCIG infusion therapy prior to the cut-off date; 23 patients died, and 81 patients were still on treatment at the end of the study. The most common reason for discontinuation was device-related problems (n=14). Other reasons included lack of efficacy (n=3), concomitant disease (n=2), progression of PD (n=2), adverse event related to surgery (n=2) and adverse event related to the drug (n=2). The demographics of all patients and of the dropout group are shown in Table 1.

The year of initiation of infusion therapy was significantly earlier among the 31 patients who discontinued treatment versus 31 matched patients.
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Table 1: Demographics of All Study Patients and Those who Dropped out of Levodopa/Carbidopa Intestinal Gel Infusion Therapy

<table>
<thead>
<tr>
<th>All patients</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>0.54</td>
<td>0.8</td>
<td></td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Age at initiation of LCIG infusion</td>
<td>60.9</td>
<td>9.4</td>
<td>60.0</td>
<td>44–76</td>
<td>31</td>
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<tr>
<td>Age at Parkinson’s disease diagnosis</td>
<td>45.2</td>
<td>9.2</td>
<td>44.0</td>
<td>30–66</td>
<td>30</td>
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<tr>
<td>Number of years since Parkinson’s disease diagnosis at initiation of LCIG infusion</td>
<td>16.0</td>
<td>6.4</td>
<td>14.5</td>
<td>6–30</td>
<td>30</td>
</tr>
<tr>
<td>Number of years on long-term LCIG infusion</td>
<td>3.2</td>
<td>2.7</td>
<td>2.3</td>
<td>0–10</td>
<td>31</td>
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</table>

<table>
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<tr>
<th>Dropouts</th>
<th>Mean</th>
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LCIG = levodopa/carbidopa intestinal gel, SD = standard deviation.

Source: Adapted from Nyholm et al., 2012.12

who continued therapy (p=0.046). On average, the dropout patients started LCIG infusion in 1999 and the continuing patients started LCIG infusion in 2002. It was found that the dose of LCIG at the last visit was significantly lower in the dropout group (59 ± 25 ml, decreased from 64 ± 24 ml at initiation) than in the continuing group (79 ± 36 ml, increased from 70 ± 23 ml at initiation; p=0.015). In addition, patients were more likely to stop treatment before 2000. The dropout rate after initiation of LCIG infusion treatment was fairly stable, with three to nine patients per 100 patient-years discontinuing the treatment.

**Patients’ View of Levodopa/Carbidopa Intestinal Gel Infusion**

In a retrospective study evaluating patients’ view of LCIG infusion therapy, patient-perceived frequency and discomfort from motor and non-motor symptoms before and after starting LCIG infusion were assessed using a questionnaire (68 patients) and a semi-structured interview (25 patients).

The results showed that after initiating LCIG infusion, there was a significant reduction in discomfort (p<0.01) for 17 of 44 symptoms. Questions concerning activities of daily living, sleep and social relations demonstrated significant improvements after the start of LCIG infusion. Moreover, 96% of the 25 patients interviewed strongly recommended the therapy to another person.

**Comparison of Levodopa/Carbidopa Intestinal Gel Infusion and Deep Brain Stimulation**

There are no direct randomised comparisons of the three CDS therapies. A retrospective study compared LCIG infusion with subthalamic nucleus deep brain stimulation (STN-DBS) in APD patients (n=20 for each therapy).13 Clinical and neuropsychological data for the two groups were compared at baseline and at follow-up. The mean follow-up for both groups was approximately 15 months. With both treatments, there were significant improvements in UPDRS-II, UPDRS-III and UPDRS-IV scores (see Figure 5) and a considerable reduction in the percentage of waking day spent in ‘off’. Only STN-DBS led to a significant improvement in dyskinesia duration and disability. However, the greater improvement in dyskinesia with STN-DBS could possibly be due to the fact that the STN-DBS patients were assessed on-stimulation and off-medication. STN-DBS was associated with a significant decrease in the phonemic verbal fluency score, while patients on LCIG infusion showed a milder worsening in this task. It was also shown that procedure-related complications were more frequent with LCIG infusion than with STN-DBS.16 There is a need for more direct comparisons between CDS therapies, and a prospective randomised comparison of LCIG and DBS is planned.

**Conclusions**

LCIG infusion therapy improves motor performance in PD patients. The long-term efficacy of LCIG infusion has been demonstrated, and data suggest patients do not develop tolerance even after several years of treatment. Furthermore, the restricted mean duration of LCIG infusion treatment is nearly 8 years, and drug dosage is stable over time. The T-port, when applied with improved implantation and gastrostomy techniques, may overcome many of the problems previously encountered with the LCIG tubing system. More data are emerging on the therapy, and our group has plans for a multicentre, randomised trial to compare LCIG infusion with STN-DBS.