Intermittent vs Continuous Levodopa Administration in Patients With Advanced Parkinson Disease

A Clinical and Pharmacokinetic Study

Fabrizio Stocchi, MD, PhD; Laura Vacca, MD, PhD; Stefano Ruggieri, MD; C. Warren Olanow, MD

Background: Levodopa-related motor complications can be an important source of disability for patients with advanced Parkinson disease. Current evidence suggests that these motor complications are related to the relatively short half-life of levodopa and its potential to induce pulsatile stimulation of striatal dopamine receptors. Motor complications can be diminished with a continuous infusion of levodopa.

Objective: To investigate the specific pharmacokinetic changes associated with the benefits of levodopa infusion.

Design: We performed an open-label study in 6 patients with Parkinson disease who experienced severe motor complications while receiving standard oral formulations of levodopa/carbidopa. Patients were subsequently treated for 6 months with continuous daytime intraintestinal infusions of levodopa methyl ester. Levodopa pharmacokinetic studies were performed at baseline and 6 months in 3 of these patients.

Results: Compared with treatment with intermittent doses of a standard oral formulation of levodopa, continuous infusion provided significant improvement in both “off periods” and dyskinesia. Results of plasma pharmacokinetic studies demonstrated that compared with oral administration, continuous levodopa infusion was associated with a significant increase in the levodopa area under the curve and avoided the low plasma trough levels seen with oral drug administration.

Conclusions: This study confirms that a continuous levodopa infusion is associated with reduced motor complications compared with the standard oral formulation of the drug in patients with advanced PD. Pharmacokinetic studies demonstrate that reduced motor complications are associated with avoiding low plasma levodopa trough levels and are not adversely affected by relatively high plasma levodopa concentrations. We propose that if levodopa/carbidopa could be administered orally in a manner that mirrors the pharmacokinetic pattern of the infusion, it might lead to a similar reduction in motor complications.

Arch Neurol. 2005;62:905-910

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EVOĐOPA-RELATED MOTOR complications (motor fluctuations and dyskinesia) can be difficult to manage and represent an important source of disability for patients with Parkinson disease (PD) (hereafter referred to as PD patients). It is currently thought that motor complications are related to abnormal, intermittent, pulsatile stimulation of denervated dopamine receptors by short-acting dopaminergic agents such as levodopa. Indeed, long-acting dopamine agonists are associated with a reduced risk of motor complications in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and PD patients. However, PD patients eventually require levodopa therapy, and the introduction of supplemental levodopa therapy is associated with an increase in the frequency of motor complications, even when the drug is administered in combination with a dopamine agonist. It has therefore been considered that more continuous delivery of levodopa might improve PD therapy and be associated with a reduced risk of motor complications. Indeed, continuous infusions of levodopa have been demonstrated to reverse established motor complications in patients with advanced PD. An oral levodopa treatment strategy that provided comparable results would be preferable; however, this has not been able to be accomplished to date. A delineation of the pharmacokinetic changes that are associated with reduced motor complications

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might serve as a template for the development of an oral levodopa treatment strategy that simulates the levodopa infusion pharmacokinetic profile and provides a similar reduction in the risk of inducing motor complications.

In the present study, we confirm that continuous intraintestinal levodopa infusion is associated with a significant reduction in "off periods" (ie, periods in the "off-medication" state) and dyskinesia in patients with advanced PD compared with standard oral formulations of the drug. We further describe the plasma pharmacokinetic profiles seen with intermittent oral and continuously infused levodopa administration and describe those pharmacokinetic features that correspond to the reduction in motor complications observed with levodopa infusion.

### METHODS

We performed a 6-month, prospective, open-label evaluation of the effects of an intraintestinal infusion of levodopa methyl ester (Chiesi Farmaceutici SpA, Parma, Italy) in 6 patients with advanced PD. Three of these 6 patients also agreed to undergo a pharmacokinetic study at baseline while receiving oral formulations of levodopa and at 6 months after treatment with continuous levodopa infusion. Patients participating in the study were diagnosed as having PD according to the London Brain Bank Criteria and were treated with only levodopa and carbidopa in stable dosages that had not been changed in the previous 30 days. Exclusion criteria consisted of atypical or secondary parkinsonism, dementia, psychosis, use of neuroleptics, clinically significant medical or laboratory abnormalities, and the use of investigational drugs within the preceding 3 months.

All patients signed an informed consent approved by the institutional review board before participation in the study. Each patient had extreme disability as a consequence of motor complications that prevented patients from performing their normal activities of daily living. In each case, these problems could not be satisfactorily controlled with manipulations of the levodopa dosage regimen or with previous trials of a variety of dopamine agonists and other antiparkinsonian drugs. Baseline characteristics of the patients are presented in Table 1. After baseline assessment, levodopa/carbidopa therapy was discontinued. Patients then started therapy consisting of oral carbidopa, 25 mg every 4 hours, and levodopa methyl ester administered via an infusion pump connected to a nasal tube placed in the duodenum under radiographic control as we have previously described. Levodopa methyl ester was used because it is highly water soluble and can be delivered in a smaller volume than regular formulations of levodopa. Levodopa methyl ester, in a concentration of 250 mg/mL, was infused continuously during the waking day for a 12-hour course at an initial infusion rate of 125 mg/h. The infusion rate was then titrated to provide optimal clinical benefit. After approximately 2 weeks, a permanent jejunostomy or a gastrostomy with a tube placed in the duodenum was performed in 3 patients each. Levodopa methyl ester was delivered by means of a portable, computerized, programmable micropump with a reservoir that could hold 10 or 20 mL. The infusion was performed between approximately 8 AM and 8 PM and was discontinued overnight. Carbidopa was administered orally at a dosage of 25 mg 4 times per day. The levodopa infusion rate could be adjusted at any time during the first 5 months of the study but was kept constant during the final 4 weeks of the study.

Patients were seen monthly after surgery for routine medical care and examination for adverse effects. Patients were admitted to the hospital at baseline and 6 months after initiating the infusion for formal evaluations. These evaluations included Unified Parkinson’s Disease Rating Scale (UPDRS) motor examination performed in the practically defined "off" state (12 hours after the evening dose of levodopa) and best "on" state (best response 1-2 hours after administration of the usual morning dose of levodopa). While the patient was in the hospital, and between the hours of 8 AM and 8 PM, the evaluating physician performed half-hourly motor assessments and recorded whether the patient was in the off, on with dyskinesia, or on without dyskinesia state. A dyskinesia score was calculated on the basis of answers to questions 32 through 34 of the UPDRS and with a modified Abnormal Involuntary Movement Scale (AIMS) as we have previously described. Physicinas and patients completed a clinical global impression rating scale at the end of the study to assess whether patients were improved compared with baseline. All study evaluations were performed by the same examiner (L.V.). A separate investigator (F.S.) performed therapeutic adjustments.

Three patients (patients 2, 3, and 4) participated in the pharmacokinetic study that was performed at the baseline visit, when patients were receiving levodopa in a standard oral formulation, and at the final visit, when they were receiving levodopa in a continuous intraintestinal infusion. Levodopa dosages were not changed for the 4 weeks before either of these evaluations. Pharmacokinetic studies were performed while patients were hospitalized and on a separate day from the motor evaluation. On the night before the pharmacokinetic study, a venous catheter was inserted into a forearm vein for blood collection. The next morning, blood samples were obtained hourly between 8

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**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y*</th>
<th>Duration of PD, y</th>
<th>Duration of Levodopa Therapy, y</th>
<th>H&amp;Y Stage</th>
<th>UPDRS (ADL)</th>
<th>UPDRS (Motor)</th>
<th>Hours in On State Without Dyskinesia</th>
<th>Total Daily Levodopa Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>On State</td>
<td>Off State</td>
<td>On State</td>
<td>Off State</td>
</tr>
<tr>
<td>1/F/58</td>
<td>28</td>
<td>20</td>
<td>5</td>
<td>9</td>
<td>21</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>2/F/63</td>
<td>16</td>
<td>14</td>
<td>5</td>
<td>9</td>
<td>22</td>
<td>46</td>
<td>28</td>
</tr>
<tr>
<td>3/F/69</td>
<td>24</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>30</td>
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<tr>
<td>4/M/31</td>
<td>12</td>
<td>11</td>
<td>5</td>
<td>8</td>
<td>25</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td>5/M/48</td>
<td>11</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>20</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>6/M/60</td>
<td>12</td>
<td>12</td>
<td>5</td>
<td>8</td>
<td>23</td>
<td>48</td>
<td>18</td>
</tr>
</tbody>
</table>

All patients signed an informed consent approved by the London Brain Bank Criteria and were treated with only levodopa and carbidopa in stable dosages that had not been changed in the previous 30 days. Exclusion criteria consisted of atypical or secondary parkinsonism, dementia, psychosis, use of neuroleptics, clinically significant medical or laboratory abnormalities, and the use of investigational drugs within the preceding 3 months.

All patients signed an informed consent approved by the institutional review board before participation in the study. Each patient had extreme disability as a consequence of motor complications that prevented patients from performing their normal activities of daily living. In each case, these problems could not be satisfactorily controlled with manipulations of the levodopa dosage regimen or with previous trials of a variety of dopamine agonists and other antiparkinsonian drugs. Baseline characteristics of the patients are presented in Table 1. **Abbreviations:** ADL, activities of daily living; H&Y, Hoehn and Yahr; NA, not applicable; on state, during good response to levodopa; off state, when drug is not working and patients are experiencing parkinsonism; PD, Parkinson disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Patients’ average age, (mean [SD]), 63.2 (11.1).
†Based on UPDRS items 32 through 34.
Table 2. Comparison of Baseline vs Final Visit Scores

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>UPDRS motor score, on state</td>
<td>24.8 ± 5.5</td>
<td>24.0 ± 4.7</td>
</tr>
<tr>
<td>UPDRS motor score, off state</td>
<td>78.5 ± 4.6</td>
<td>77.9 ± 4.9</td>
</tr>
<tr>
<td>UPDRS ADL score, on state</td>
<td>21.8 ± 1.9</td>
<td>16.3 ± 1.9</td>
</tr>
<tr>
<td>Time in off state, h/d</td>
<td>7.8 ± 0.8</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Dyskinesia score (AIMS range, 0-5)</td>
<td>4 ± 0.8</td>
<td>1 ± 0.9</td>
</tr>
<tr>
<td>Dyskinesia score (UPDRS items 32-34)</td>
<td>8.8 ± 0.7</td>
<td>3.1 ± 0.7</td>
</tr>
<tr>
<td>Daily levodopa dose, mg</td>
<td>1233 ± 98.3</td>
<td>1224 ± 246.5</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; AIMS, Abnormal Involuntary Movement Scale; on state, during good response to levodopa; off state, when drug is not working and patients are experiencing parkinsonism; UPDRS, Unified Parkinson’s Disease Rating Scale.

AM and 8 PM. Venous blood samples (4 mL) were collected in heparinized test tubes (Vacutainer; Becton, Dickinson and Company, Mountain View, Calif) and inverted gently several times to ensure proper mixing with the anticoagulant. Care was taken to avoid prolonged contact of the sample with the rubber stopper. Tubes were placed upright in a test tube rack, surrounded by ice, protected from light, centrifuged, and stored at −80°C. All samples were analyzed using standard high-pressure liquid chromatography with electrochemical detection using an ESA 5300 system (ESA Inc, Chemsford, Mass) and standard control samples as previously reported by our group.21,22 Baseline samples were evaluated as a group, and 6-month samples were evaluated as a separate group.

We performed statistical analyses using the 2-tailed t test for continuous or normalized data and nonparametric tests (Wilcoxon signed rank test) for other analyses. Unless otherwise indicated, mean values are expressed as mean ± SD.

RESULTS

CLINICAL RESULTS

Each of the 6 patients completed the 6-month trial. The surgical procedure was well tolerated in each instance and no clinically significant perioperative adverse events were encountered. The results are summarized in Table 2. In comparison with baseline, when patients were treated with a standard oral formulation of levodopa, levodopa infusion was associated with a significant improvement in off time, on time without dyskinesia, and dyskinesia score as rated by the UPDRS and a modified AIMS. The number of off hours during the 12-hour assessment period was reduced from a mean of 7.8 ± 0.8 hours at baseline to 1.7 ± 0.5 hours at 6 months (78.2% reduction; P <.001). The on time without dyskinesia was similarly improved from a mean of 0.3 ± 0.5 hour at baseline to 9.4 ± 0.8 hours at 6 months (P <.001). The dyskinesia score based on the answers to questions 32 through 34 of the UPDRS was significantly improved, falling from a mean of 8.8 ± 0.7 at baseline to 3.1 ± 0.7 at the 6-month visit (P <.001). Similar improvement was noted in the AIMS score. The UPDRS motor scores in the practically defined off state and best on state were not changed, but ADL scores in both the on and off states were significantly improved after the change to a levodopa infusion. The baseline and 6-month scores for the number of hours in the off state and the dyskinesia score for the individual patients are shown in Figure 1.

Each patient experienced dyskinesia that began approximately 20 minutes after the infusion was discontinued and lasted for approximately 30 minutes. These were primarily dystonic, were stereotypic, and predominantly affected the lower extremities. Thereafter, patients experienced worsened mobility and were relatively off, ie, parkinsonian, for the remainder of the night but were nonetheless able to sleep uneventfully. Full benefits resumed approximately 15 minutes after starting the infusion in the morning. This pattern was present almost every night and did not change during the study. Investigator and patient clinical global impression ratings were markedly improved at the final visit compared with baseline for each patient.

Patients noted reduced off time almost immediately (within days) after the introduction of the infusion. Improvement in dyskinesia occurred more gradually, with full benefit not occurring for approximately 6 to 8 weeks. Some worsening of dyskinesia occurred initially in sev-
eral patients. Benefits in off time and dyskinesia were maintained during the 6-month duration of the trial.

The mean daily levodopa methyl ester dosage infused at 6 months was $1224\pm246.5$ mg and was not significantly different from the mean dosage of regular levodopa used at baseline ($1233\pm98.3$ mg/d). The levodopa infusion initiated rate was 125 mg/h at baseline and 102 mg/h at the end of the study, with most of the adjustment occurring during the first month. Patients took no other antiparkinsonian drugs during the study. Overall, the treatment was well tolerated and no patient dropped out of the study. Three patients had mild hallucinations at night that were satisfactorily treated with 12.5 mg of clozapine at bedtime. No other adverse event occurred in more than 1 patient, and there were no serious or severe adverse events.

### PHARMACOKINETIC RESULTS

Pharmacokinetic studies were performed in 3 patients at baseline when they were receiving standard oral formulations of levodopa/carbidopa and at the final visit after 6 months of treatment with continuous levodopa infusion. The group results are provided in Table 3, and the individual pharmacokinetic patterns are illustrated in Figure 2. The plasma levodopa area under the curve was increased by a mean of 214% after infusion of levodopa ($P=0.02$). Levodopa infusion was also associated with a significant increase in mean plasma levodopa concentration ($P=0.02$). The maximal plasma levodopa concentration was higher with infusion than with oral delivery but failed to meet significance ($P=0.09$). On the other hand, the minimal plasma levodopa concentration was much higher when levodopa was infused than after intermittent oral dosing ($2488$ vs $500$ ng/mL; $P=0.03$). No significant change in the variability of the plasma levodopa levels (the difference between the maximal and minimal plasma levodopa concentrations) between the different routes of drug administration was observed.

### COMMENT

We herein confirmed, in an open-label trial, earlier reports indicating that continuous intraintestinal infusion of levodopa reduces motor complications in patients with advanced PD. We observed that in comparison with a standard oral formulation of levodopa, continuous levodopa infusion significantly improved the number of off hours, the number of on hours without dyskinesia, and dyskinesia severity. The UPDRS activities of daily living scores were improved, likely reflecting the reduction in off time.

### Table 3. Mean Levodopa Plasma Pharmacokinetics in 3 Patients

<table>
<thead>
<tr>
<th>Levodopa Concentration</th>
<th>Oral Therapy</th>
<th>Infusion</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa AUC, ng/mL per hour</td>
<td>16 384 ± 2712.4</td>
<td>35 081.3 ± 5223.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Plasma levodopa concentration, ng/mL</td>
<td>1508.4 ± 230.9</td>
<td>3103.3 ± 450.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>3207 ± 897.1</td>
<td>4576 ± 912.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>506.7 ± 161.7</td>
<td>2488 ± 522.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Maximum levodopa concentration variance, Cmax − Cmin</td>
<td>2700.3 ± 1015.3</td>
<td>2088 ± 937.0</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; Cmax, maximum plasma levodopa concentration; Cmin, minimum plasma levodopa concentration.

*Unless otherwise indicated, data are expressed as mean ± SD.
and dyskinesia. There was no change in UPDRS motor scores in the practically defined off state or best on state, indicating that there was no tolerance. Comparable benefits were observed in each patient, and adverse events were not a problem. Infusions were restricted to approximately 12 h/d to diminish the risk of inducing tolerance and psychiatric adverse effects that have been reported with around-the-clock infusions.22,23 Patients experienced transient dyskinesia when the infusion was discontinued. This likely represents a form of diphasic dyskinesia due to falling dopaminergic levels. They also experienced off periods during the night (not scored) but these were tolerable, and global clinical assessments by both patients and physicians indicated that patients had experienced marked improvement in overall function in comparison with baseline.

In 3 patients, pharmacokinetic studies were performed at baseline, when they were receiving a standard oral formulation of levodopa and had severe motor complications, and then again at the final visit after 6 months of levodopa infusion, when motor complications were significantly improved. Results of these studies demonstrate that levodopa infusion avoids the low trough levels observed with oral delivery of a standard formulation of levodopa and that mean plasma levodopa concentration and the area under the curve are significantly increased, despite the improvement in dyskinesia.

Current evidence indicates that under normal circumstances, nigral neurons fire continuously and striatal dopaminergic receptors are exposed to relatively constant levels of dopamine.25 Motor complications associated with standard levodopa therapy are thought to be related to a change in this pattern with the development of abnormal pulsatile stimulation of striatal dopamine receptors due to intermittent administration of a drug such as levodopa with a relatively short half-life.3,20 In dopamine-lesioned rodents, intermittent dosing with standard oral levodopa is associated with a progressive shortening of the duration of the motor response, whereas this does not occur if animals are treated with a continuous levodopa infusion.27 Studies in MPTP-treated nonhuman primates similarly note that short-acting dopaminergic agents such as levodopa are associated with a greater frequency and severity of dyskinesia than are long-acting or more continuously administered dopaminergic agents.28 Indeed, dyskinesias in MPTP-treated monkeys are more frequent and more severe when a short-acting agent is administered intermittently than when the same agent is given continuously by infusion.29 These findings suggest that motor complications are related to intermittent, pulsatile stimulation of dopamine receptors and that motor complications are less likely to develop when dopaminergic therapies are delivered in a more continuous manner.30 Indeed, prospective double-blind controlled studies demonstrate reduced motor complications when therapy for PD is initiated with a long-acting dopamine agonist compared with a standard formulation of levodopa.9,19 Furthermore, several studies have reported a reduction in off time and/or dyskinesias with continuous delivery of levodopa or a dopamine agonist such as apomorphine hydrochloride or lisuride.11-18,20,23,24,31-35 Our study provides further support for the observation that continuous infusion of a dopaminergic therapy reduces motor complications in patients with advanced PD. In addition, our study further illustrates that motor complications can be reversed by continuous administration of the same dopaminergic agent that induces them when administered in a pulsatile manner.

We designed the study to define the differences in the plasma levodopa pharmacokinetic profiles between treatment with a standard oral formulation of levodopa that is associated with a high frequency of motor complications and treatment with a continuous intraintestinal levodopa infusion that is associated with a marked reduction in motor complications. We observed a significant increase in the minimal plasma levodopa trough level when patients were treated with continuous levodopa infusion. We postulate that the low trough levels seen with intermittent administration of standard oral formulations of levodopa cause striatal dopamine receptors to be periodically deprived of dopaminergic stimulation with consequent plastic changes in intracellular signals and neuronal firing patterns leading to motor complications. In contrast, levodopa infusion avoids low plasma trough levels and may thus result in more constant activation of brain dopamine receptors with a reduced risk of motor complications. The mean plasma levodopa concentration and area under the curve were significantly increased after levodopa infusion, despite the observation that this treatment was associated with a dramatic reduction in both off time and dyskinesia. Peak levodopa concentrations were also higher with continuous levodopa infusion, although this failed to reach statistical significance. The higher levodopa concentrations could have accounted for the reduction in off time, but would not account for the corresponding reduction in dyskinesia. These findings seemingly contradict the popular notion that increased amounts of levodopa are associated with increased dyskinesias36 and support the concept that it is the manner in which levodopa is administered rather than the absolute concentration that is the more critical. These studies also suggest that it may not be necessary to maintain the plasma levodopa concentration at an absolutely constant level, avoiding fluctuations in plasma concentration, to minimize the risk of motor complications. Rather, the reduced motor complications associated with continuous levodopa infusion appear to be related primarily to avoiding low trough levels and maintaining the levodopa concentration above a minimal threshold level that is sufficient to provide continuous activation of dopamine receptors. This concept could explain why trials with controlled-release formulations of levodopa failed to reduce motor complications.37,38 As the low-dose frequency used and the erratic absorption of these agents may not have eliminated the high peaks and the low trough levels associated with the development of motor complications.

This plasma pharmacokinetic profile may be easier to replicate with oral dopaminergic strategies than the constant level that has previously been considered necessary to provide continuous dopaminergic stimulation.26 We postulate that the development of an oral levodopa treatment strategy that avoids low trough levels may simulate...


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