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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Continuous Versus Intermittent Oral Administration of Levodopa in Parkinson's Disease Patients With Motor Fluctuations: A Pharmacokinetics, Safety, and Efficacy Study

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ABSTRACT

Background: Laboratory and clinical evidence indicate that continous delivery of levodopa is associated with reduced motor complications compared to standard intermittent levodopa.

Objective: To assess the pharmacokinetics and efficacy of continuous oral delivery of L-dopa/carbidopa in PD patients with motor fluctuations.

Methods: Eighteen PD patients with motor fluctuations were enrolled in an open-label study comparing pharmacokinetics and efficacy measures between standard intermittent oral L-dopa/carbidopa and "continuous" oral L-dopa/carbidopa. Continuous treatment was operationally defined as sips of an L-dopa dispersion at 5- to 10-minute intervals. On day 1, patients received their usual oral L-dopa/carbidopa doses. On day 2, patients received L-dopa/carbidopa dose by "continuous" oral administration. On day 3, patients received *a single* dose of oral L-dopa/carbidopa followed by continuous

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administration of L-dopa/carbidopa. Each study period was 8 hours, and the total L-dopa/carbidopa dose administered was the same on each day. Analyses of variability were primarily-based samples drawn between 4 and 8 hours when subjects were in a relative steady state.

Results: There was less variability in plasma L-dopa concentration with continuous versus intermittent oral L-dopa/carbidopa treatment (fluctuation index was 0.99 ± 0.09 vs. 1.38 ± 0.12 [$P < 0.001$] and coefficient of variation was 0.35 ± 0.03 vs. 0.49 ± 0.04 [$P < 0.001$]). Mean OFF time was decreased by 43% ($P < 0.001$) with continuous oral L-dopa therapy. No safety or tolerability issues were observed.

Conclusions: Continuous oral delivery of L-dopa/carbidopa was associated with less plasma variability and reduced off time in comparison to standard intermittent oral L-dopa/carbidopa therapy. © 2019 International Parkinson and Movement Disorder Society

Key Words: continous levodopa; motor complications; Pharmacokinetics

Chronic levodopa treatment is associated with development of potentially disabling motor complications in the majority of Parkinson's disease (PD) patients. Increasing evidence suggests that these are related to the nonphysiological restoration of brain dopamine with intermittent administration of standard oral L-dopa.[1] It has been hypothesized that continuous delivery of L-dopa could restore brain dopamine in a more physiological manner and prevent or reverse motor complications. This concept was supported by a double-blind trial demonstrating that continuous intraintestinal infusion of L-dopa is associated with reduced "off" time and increased "on" time without dyskinesia in comparison to optimized standard oral L-dopa.[2] However, this procedure is associated with potentially serious adverse events, and an intestinal infusion is cumbersome. Accordingly, there has been an active effort to develop alternate methods for providing continuous L-dopa availability.[3] Three decades ago, Kurlan and colleagues noted that continuous infusion of L-dopa into the stomach was associated with more stable plasma L-dopa levels than standard intermittent oral doses of L-dopa/carbidopa (LD/CD).[4] In the present trial, we compared the pharmacokinetics (PK), safety, tolerability, and efficacy of L-dopa treatment in patients with advanced PD complicated by motor fluctuations when the drug was delivered orally with standard intermittent doses or in a "continuous" manner. For purposes of this study, continuous was operationally defined as sips of an L-dopa dispersion every 5 to 10 minutes.

Patients and Methods

Eligible patients were men or women of any race aged 35 to 75 years with a diagnosis of PD consistent with UK Brain Bank criteria[5] who were on stable doses of L-dopa, suffered at least 2 hours of off time per day, and signed an institutional review board (IRB)-approved informed consent. The study was designed as an open-label 3-day trial. On each study day, patients were admitted to the clinic in the practically defined off state and treated for an 8-hour study period as follows: day 1: Subjects were treated with their usual regimen of standard intermittent oral LD/CD; day 2: Subjects were treated with continuous intra-oral LD/CD at a total dose equal to that administered on day 1; and day 3: Subjects were treated with their usual morning oral dose of standard LD/CD followed by continuous intra-oral LD/CD with the same total dose as on days 1 and 2.

Continuous LD/CD was administered as a dispersion that was freshly produced hourly by chopping up Sinemet tablets and mixing in 50 mL of neutral pH water without an aqueous buffer. The dispersion was stored in a refrigerator and shaken before each administration; the precise dose was then drawn into a syringe and administered as a sip at approximately 5- to 10-minute intervals. The total dose of LD/CD for each patient administered during the 8-hour study period was the same on each of the treatment days.

On days 1 and 2, PK assessments of plasma L-dopa concentration were performed at predose and at 30-minute intervals throughout the 8-hour study period. On days 1 and 3, an independent investigator assessed motor status and dyskinesia predose and at 30-minute intervals throughout the study period. UPDRS part III (motor examination) was performed predose and at 2, 4, and 8 hours postdose. Safety and oropharyngeal assessments were performed on each day. PK analyses were performed as previously described.[5] All samples were analyzed at the same time using standard high-pressure liquid chromatography with electrochemical detection.

Statistical Analyses

All subjects were included in the safety and efficacy analyses. The primary endpoint for the PK study was the fluctuation index (Cmax-Cmin)/Caverage) for the L-dopa plasma concentration comparing day 1 versus day 2. Because steady-state plasma L-dopa levels were not anticipated to be achieved during the first 4 hours of treatment with continuous oral administration, the fluctuation index was evaluated between hours 4 and 8. The fluctuation index was also assessed at hourly intervals as a sensitivity analysis. An additional sensitivity analysis assessed variation from linearity based on a linear regression model. Secondary endpoints included the coefficient of

TABLE 1. PK parameters (8 hours) and tests of linearity

Parameter		Intermittent L-dopa (Day 1, N = 18) Mean (SEM)		Continuous L-dopa (Day 2, N = 18) Mean (SEM)
AUC_{0-8h} (h × ng/mL)		4,522 (676)		4,387 (609)
C_{max} (ng/mL)		1,207 (146)		1,148 (164)
Fluctuation index ($_{4-8h}$)		1.38 (0.12)		0.99 (0.09)[a]
Coefficient of variation($_{4-8h}$)		0.49 (0.04)		0.35 (0.03)[a]
Treatment	**Parameter**	**Estimate**	***P* Value**	**Comment**
Intermittent L-dopa (day 2)	Intercept of linear term	148.3	<0.001	Linearity is not shown (quadratic term is significant)
	Intercept of quadratic term	–13.6	<0.001	
Continuous L-dopa (day 3)	Intercept of linear term	172.6	<0.001	Linearity is shown (quadratic term non-significant)
	Intercept of quadratic term	-8.9	0.061	

[a]$P < 0.001$ in comparison to intermittent L-dopa.

variation (standard deviation [SD]/mean of the L-dopa concentrations), area under the curve (AUC), and Cmax. Statistical analyses were performed using the two-tailed *t* test for continuous data and Wilcoxon signed-rank test for noncontinuous data. Unless indicated, mean values are expressed as ± SD.

The primary endpoint for efficacy was the change in OFF time between the two treatment regimens (day 1 vs. day 3). Secondary endpoints included ON time without severe dyskinesia and change from predose in UPDRS motor score. Analyses were performed using a mixed model for repeated measures with baseline assessment as a covariate. Because this was a pilot study, nominal *P* values are provided with no adjustment for multiple comparisons. Safety was assessed descriptively, and tolerability by percentage of completers.

A sample size of 18 patients provided >90% power to detect a difference in fluctuation index of 25%, with an SD of 25% and alpha = 0.05. This sample size provided >80% power to detect a reduction in "OFF" time of 1.4 hours with SD of 2 and alpha = 0.05.

The study was funded by Synagile Corp, and registered at ClinicalTrials.gov (NCT02763137).

Results

Eighteen patients met eligibility criteria, signed IRB-approved informed consent, and completed the study. Baseline demographics are provided in Supporting Information Table S1. Subjects had a mean of 4.4 hours of OFF time per day and a mean UPDRS part III score of 42.2. There were no serious or clinically significant adverse events. There were no specific oral complaints or findings, and there were no tolerability issues.

The average L-dopa dose delivered over the 8-hour study period was 456 ± 33, 467 ± 37, and 463 ± 32 mg on days 1, 2, and 3, respectively. A summary of PK data is provided in Table 1. The fluctuation index from 4 to 8 hours (the primary endpoint) was significantly reduced with continuous versus intermittent L-dopa delivery (0.99 ± 0.09 vs. 1.38 ± 0.12; $P < 0.001$). The mean plasma concentration for the group and a representative patient example are provided in Figure 1. Note that patients were not on a fixed dose or dosing frequency of L-dopa, which explains why results of reduced variability are more clearly demonstrated in the individual patient example than in the group showing the mean concentrations. The fluctuation index calculated at 1-hour intervals demonstrated reduced variability with continuous versus intermittent oral delivery with an overall *P* value <0.001 (Fig. 1B). Continuous, but not intermittent, oral, L-dopa delivery also met criteria for linearity and showed significantly less variability from a regression line ($P < 0.01$). There was also a reduction in the coefficient of variability with continuous versus intermittent oral delivery ($P < 0.001$).

The results of the efficacy assessments comparing day 1 (intermittent oral L-dopa) and day 3 (single oral dose followed by continuous oral L-dopa) are presented in Table 2. Continuous oral administration was associated with a reduction in OFF time normalized to a 16-hour waking day of approximately 1.9 hours ($P < 0.001$) and an increase in ON time without severe dyskinesia of 1.1 hours ($P = 0.101$); OFF time was reduced in all but 3 of 18 subjects and not increased in any. Continuous oral treatment was also associated with lower UPDRS scores at each time point measured and reached significance at 2 hours postdosing (Table 2). Three patients required apomorphine subcutaneous doses to facilitate turning ON—but required this with both intermittent and continuous LD/CD treatment.

Discussion

We demonstrate that in comparison to standard intermittent oral LD/CD therapy, continuous oral

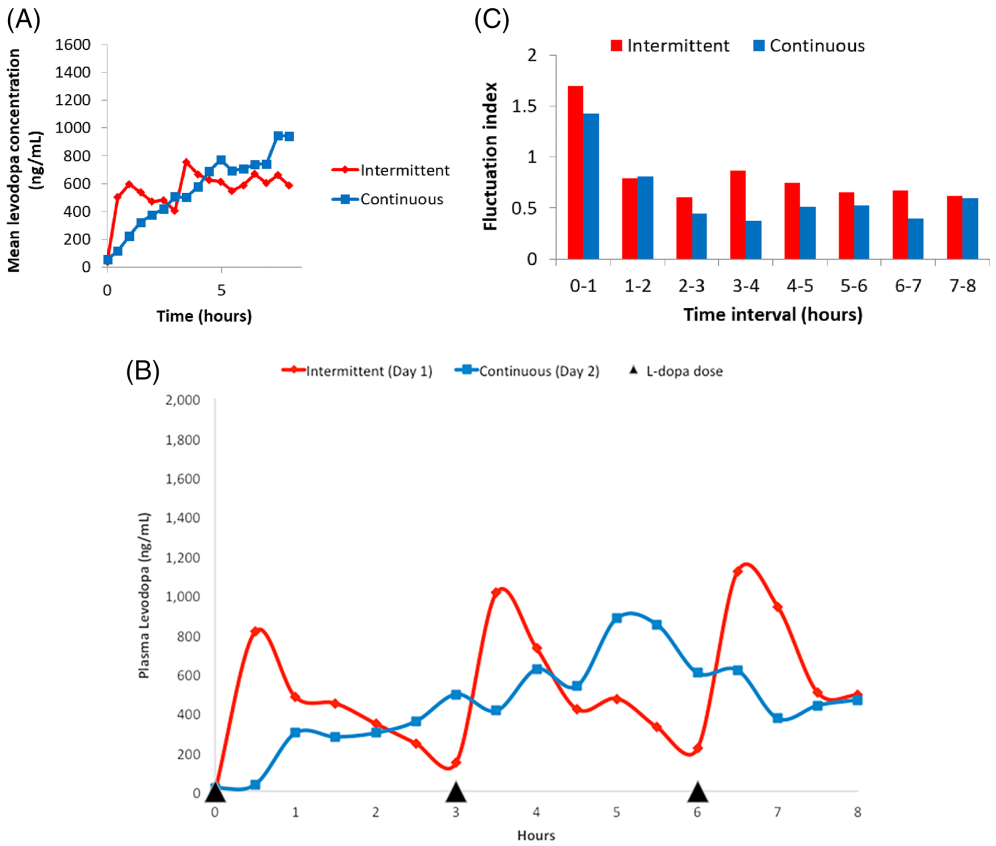

FIG. 1. (A) Mean plasma L-dopa concentrations (ng/mL) for administration of intermittent (red) and continuous (blue) oral LD/CD over the 8-hour period of the study. Note that even though steady state is not achieved, there is a reduction in variability with continuous delivery. This is better illustrated by statistical calculations given that patients were not on a fixed dose or dose regimen. (B) Plasma L-dopa levels following administration of standard intermittent oral (red) and continuous oral (blue) LD/CD in a representative PD individual. Note that continuous oral delivery avoids the marked fluctuations and the periodic low trough levels associated with intermittent oral delivery. (C) Fluctuation index of continuous versus intermittent L-dopa calculated at 1-hour intervals. Note the reduction in variability with continuous oral delivery at most time intervals, particularly after hour 2. [Color figure can be viewed at wileyonlinelibrary.com]

delivery of LD/CD is associated with reduced variability in plasma L-dopa concentration and avoids the relatively low trough levels thought to contribute to the development of motor complications.[5] Reduced variability was observed with the prespecified primary endpoint (fluctuation index), sensitivity analyses (variability in hourly measures and in linearity on a linear regression model), and the secondary endpoint (coefficient of variation). In addition, based on open-label evaluations, continuous oral infusion was associated with significant benefits in OFF time and UPDRS score. It should be noted that as in the clinical setting, we used a standard dose of LD/CD in the AM followed by continuous oral LD/CD in order to facilitate turning ON in the morning, and this extra L-dopa may have contributed to the improvement in UPDRS and OFF scores. However, the total L-dopa

TABLE 2. Clinical endpoints

Clinical Assessment	Endpoint	Intermittent L-dopa (Day 1) Mean (SEM)	AM Dose + Continuous L-dopa (Day 3) Mean (SEM)	*P* Value Versus Day 1
UPDRS part III motor score	Predose score	42.2 (2.4)	42.0 (2.0)	—
	Change from baseline to 2 hours post-AM dose	−18.4 (2.3)	−20.6 (1.9)	0.035
	Change from baseline to 4 hours post-AM dose	−18.8 (2.0)	−21.9 (1.5)	0.073
	Change from baseline to 8 hours post-AM dose	−20.0 (1.6)	−21.1 (1.8)	0.255
Motor atate[a]	OFF time (hours)	4.39 (0.59)	2.50 (0.43)	<0.001
	ON time without severe dyskinesia (hours)	11.61 (2.52)	12.72 (3.10)	0.101

Data shown as descriptive statistics (mean [SD]) and *P* values calculated with mixed model for repeated measures.
[a]PD motor state was normalized to 16 waking hours.
Abbreviation: SEM, standard error of mean.

delivered over the 8-hour study period was the same in both groups, and we postulate that benefits observed also related to the more continuous availability of L-dopa with continuous oral delivery. There were no safety or tolerability issues.

Continuous oral L-dopa/delivery was delivered using precisely calculated aliquots of an L-dopa dispersion administered at 5- to 10-minute intervals. Care was taken to ensure that the same total dose of L-dopa was administered over the 8 hours of the study period on each day. PK analyses demonstrated reduced plasma L-dopa variability, and individual patients showed a pattern similar to what we have observed with continuous intestinal infusion[5]—a pattern we have not been able to achieve with oral doses of standard LD/CD, even when administered at hourly intervals. As noted in Figure 1, with continuous delivery, plasma L-dopa levels rise gradually and take several hours to reach steady state. This is why on day 3 we administered the early morning bolus to facilitate turning ON, but the total dose administered over the 8-hour study period was the same as on other days.

It is interesting to speculate on how continuous oral delivery of L-dopa might avoid the variability in gastrointestinal transit and absorption observed with standard intermittent oral dosing. First, standard LD/CD is administered as a solid tablet that must dissolve in the stomach before it can be transmitted to the jejunum for absorption; we administered L-dopa as a liquid dispersion. Several studies have demonstrated that gastric emptying of liquids is more rapid and predictable than solids.[6,7] Second, standard LD/CD is administered as an acid salt; we administered L-dopa in a dispersion with a pH of approximately 7. Chaw and colleagues demonstrated that the pH of a gastrically infused solution markedly affects gastric transit time.[8] When the gastric pH is 3, the mean residence time of liquids in the stomach was 35 to 47 minutes whereas it was 14 to 22 minutes when the gastric pH was maintained at 7. Similarly, Bianchine and colleagues noted increased L-dopa absorption in the presence of antacids.[9] These differences in pH and solidity may have accounted for a more rapid and predictable transit of L-dopa to the jejunum and more continuous absorption. Furthermore, rapid transit through the stomach might have limited the conversion of L-dopa to dopamine in the stomach and thereby reduced dopamine-mediated activation of gastric dopamine receptors, which inhibit gastric motility.[10] Our results are consistent with the findings of Kurlan and colleagues, who also noted less variability in plasma L-dopa levels with continuous infusion compared to intermittent oral delivery.[4] Similar benefits have also been reported in a small number of patients when a liquid L-dopa solution was administered hourly in combination with ascorbic acid.[11]

Our study was performed as an open-label trial, and clinical data must be interpreted in this light. However, PK assessments are objective and were performed by technicians who were not aware of study treatments. It should be noted that patients were not on a fixed dose or dosing regimen, but this is addressed in the statistical analysis, which assesses the mean of the difference in variability in the two groups. A double-blind, placebo-controlled study to assess continuous LD/CD oral delivery using a small intra-oral pump is currently underway.

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Supporting Data

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