A Phase 2a study of standard administration versus continuous intra-oral administration of levodopa/carbidopa in patients with advanced Parkinson's disease

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INTRODUCTION

As Parkinson's disease (PD) progresses it becomes increasingly difficult to control PD-associated motor symptoms with drug therapy. The therapeutic goal is to achieve a near-constant level of dopamine in the brain, requiring a near-constant level of levodopa (LD) in plasma. Although LD is widely recognized as the most efficacious treatment for PD symptoms, LD is quickly broken down in the body and its absorption can be unpredictable leading to widely varying plasma LD concentrations over the course of the day. Among patients with advanced PD, low plasma LD concentrations typically result in OFF time while high concentrations often result in dyskinesia.[1] Continuous administration of levodopa/carbidopa (LD/CD) via duodenal infusion dramatically reduces motor fluctuations but requires surgical implantation of a PEG tube, has a high rate of adverse events, and is inconvenient.[2] Since relief of motor complications is an important and largely unmet need facing patients with PD, we investigated whether continuous, intraoral delivery of LD/CD (CIO LD/CD) would safely reduce variability in plasma LD concentrations and reduce OFF time in fluctuating PD patients.

OBJECTIVES

- **Pharmacokinetics (PK):** compare the variability of the PK of CIO LD/CD vs. intermittent oral administration of LD/CD.
- **Motor status:** compare the effect on PD motor status (OFF, ON without severe dyskinesia, or ON with severe dyskinesia) of CIO LD/CD vs. intermittent oral administration of LD/CD.
- **Safety and tolerability:** assess safety and tolerability of CIO LD/CD.

PATIENTS AND METHODS

Patients and study design

Eighteen PD patients with motor fluctuations on stable doses of standard LD/CD ± other dopaminergic therapy (e.g., COMT inhibitors), who met entry criteria and signed an IRB-approved informed consent, participated. This was a single-center, open label study conducted in an inpatient clinical setting (IRCCS San Raffaele, Rome). Study design is shown in Figure 1.

Day 1: Enrolled subjects admitted for clinical lab evaluations. Standard oral LD/CD medication stopped at midnight.

Day 2 ("Control Day"): After breakfast, standard oral LD/CD treatment initiated. Plasma levels of LD and patient's motor status measured every 30 minutes for 8 hours. UPDRS motor exams performed by a neurologist at 0, 2, 4, and 8 hours. A standard low protein lunch provided at about hour 4.

Day 3 ("PK Day"): After breakfast, continuous intra-oral administration of LD/CD was initiated for 8 hours at the same total 8-hour dose as Day 2. Same PK blood sampling and lunch as on Day 2.

Day 4 ("Efficacy Day"): After breakfast, a morning dose of Sinemet™ (same as first dose on Day 2) was administered orally as a bolus to turn the patient ON. The remainder of the 8-hour dose (same total 8-hour dose as Days 2 and 3) was administered via continuous intra-oral administration over the course of 8 hours. Motor status assessments, UPDRS motor exams, and lunch as on Day 2.

Day 18: Patients returned to clinic for safety evaluation.

Figure 1. Flow chart of the study design.

Standard oral LD/CD treatment was defined as treatment with Sinemet™ tablets at the patient's usual pre-baseline doses and dose intervals. Continuous intra-oral administration was defined as administration of a LD/CD suspension into the mouth every 5 minutes during hours 0-3 and every 10 minutes during hours 3-8, using an oral syringe. The suspensions were prepared every hour by dispersing Sinemet™ tablets in water (one 100/25 LD/CD tablet per 50 mL water). The suspensions were shaken prior to each administration to ensure homogeneity. Each patient's total LD/CD dose during the 8-hour observation period was the same on all three days.

Statistical analysis

Primary endpoint (PK)

1. Variability in plasma concentrations of LD, as assessed by linear regression and by fluctuation index ((C_{max} - C_{min})/$C_{average}$) on Days 2 (tablet) and 3 (CIO).

Secondary Endpoints

1. Efficacy: OFF time and UPDRS Part III over 8 hours on Days 2 (tablet) and 4 (morning bolus + CIO).
2. PK: Variability using coefficient of variation (CV).
3. Safety and tolerability: adverse events, clinical laboratory test results, vital signs results, physical and neurological examination, ECG, and oral site assessments.

Exploratory measures: levodopa C_{max}, T_{max}, and AUC.

RESULTS

Mean plasma levodopa concentrations for Day 3 (CIO LD/CD) are shown in Figure 2.

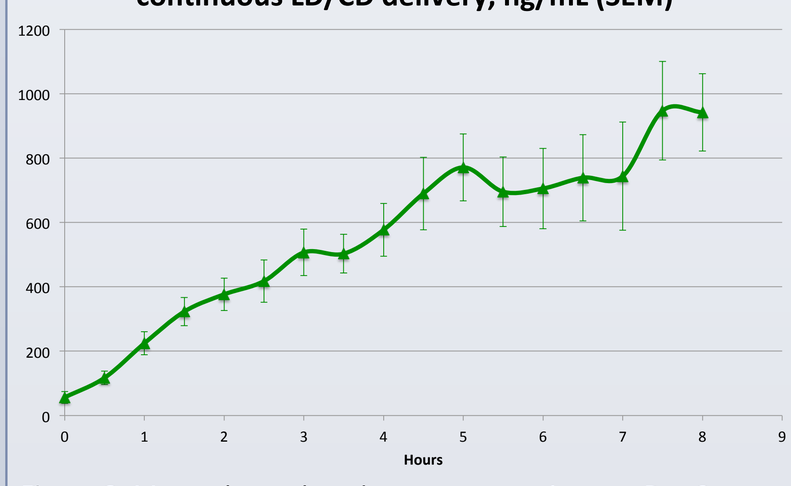

Figure 2. Mean plasma levodopa concentrations on Day 3.

Continuous intra-oral administration of LD/CD over the course of 8 hours significantly reduced (p = 0.0004) the variability of plasma LD concentrations as assessed by the fluctuation index (Figure 3).

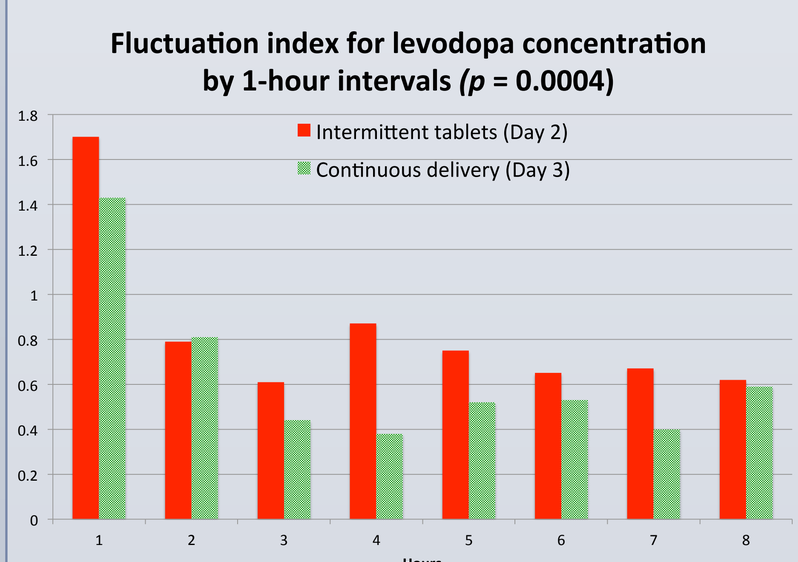

Figure 3. Mean fluctuation index of LD plasma concentrations at 1-hour intervals for intermittent LD/CD and for CIO LD/CD.

The linearity of the PK was superior for CIO LD/CD (r^2 = 0.05) versus intermittent oral LD/CD (r^2 = 0.46) (p < 0.001). Likewise, the mean CV by 1-hour intervals was lower with CIO LD/CD versus intermittent oral LD/CD (p = 0.0006).

OFF time was reduced by 43% over the 8-hour observation period, from 2.19±0.30 to 1.25±0.21 hours (mean±SEM) (p < 0.001) (Figure 4). A non-significant increase in severe dyskinesia was almost entirely attributable to a single patient with diphasic dyskinesia.

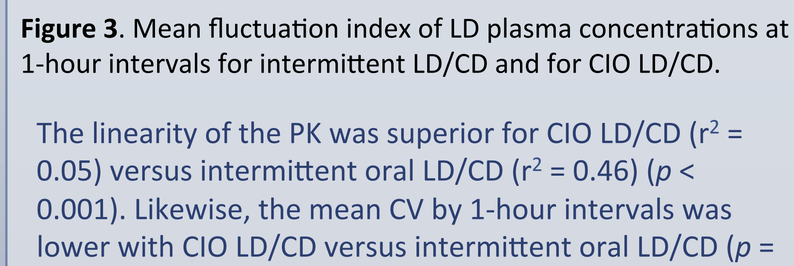

Figure 4. Distribution of motor states for intermittent LD/CD and for CIO LD/CD.

Off time was reduced in 15 patients, remained the same in 3 patients, and increased in 0 patients (Figure 5).

The average UPDRS part III motor score at 2, 4 and 8 hours was improved with CIO LD/CD by -2.1±0.7 (p = 0.010).

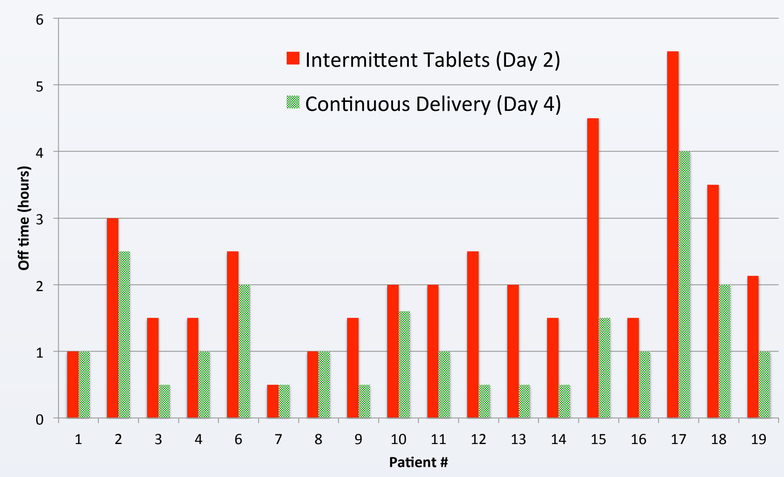

Figure 5. Change in OFF time for individual patients.

The PK of an exemplary patient is shown in Figure 6.

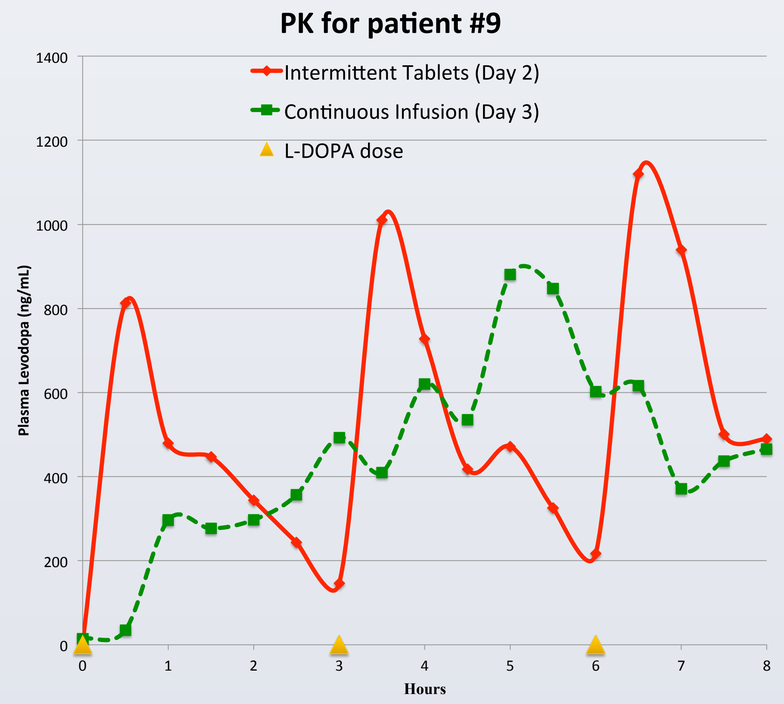

Figure 6. PK for an exemplary patient.

No treatment-related adverse events were observed. There were no tolerability issues of any severity, as assessed by oral site assessments by physicians and by patients.

CONCLUSIONS

All primary and secondary endpoints of the Phase 2a trial were met, establishing that continuous intraoral delivery of LD/CD results in reduced plasma LD variability, reduced OFF time, and improved UPDRS part III motor scores as compared to standard intermittent oral LD/CD tablet therapy. The 43% reduction in OFF time was highly clinically significant to patients with advanced PD. There were no treatment-related adverse events nor were there any tolerability issues of any severity.

The results suggest that continuous oral infusion of LD/CD may constitute a safe, noninvasive approach for reducing OFF time in patients with advanced PD. The results need to be confirmed in a double blind trial.

Based on the results of this Phase 2a study, synAgile Corporation is developing DopaFuse™, a product that will noninvasively and continuously deliver a concentrated suspension of LD/CD into the mouth. The system consists of a miniature, disposable, drug delivery device carried on a small, tooth-attached retainer. The LD/CD is swallowed with the patient's saliva and absorbed via the conventional gastrointestinal route. The drug formulation has no taste and the infusion is imperceptible to the patient. The delivery system is not visible to others, is comfortable to wear, and does not interfere with speech, swallowing, or drinking. It is expected to provide PD patients in need of deep brain stimulation or LD/CD duodenal infusion with a safe, more convenient, noninvasive therapy option to reduce their motor complications.

REFERENCES

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