Comparison of Orally Dissolving Carbidopa/Levodopa (Parcopa) to Conventional Oral Carbidopa/Levodopa: A Single-Dose, Double-Blind, Double-Dummy, Placebo-Controlled, Crossover Trial

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Abstract: Levodopa use in fluctuating Parkinson’s disease (PD) is complicated by an inconsistent and prolonged onset to clinical improvement. An orally dissolved carbidopa/levodopa (OD C/L) preparation (Parcopa UCB Pharma) is available in the United States. This offers potential advantages to shorten the duration from ingestion to clinical improvement. Surprisingly, this has never been clinically assessed. We tested 20 patients with fluctuating PD and a Unified Parkinson’s Disease Rating Scale (UPDRS) “off” motor score of ≥25 in a 2-day, single-dose, double-blind, double-dummy, crossover study. Patients arrived in the morning in the practically defined “off” state and were randomly assigned to receive identical doses of either oral C/L and OD placebo or OD C/L and oral C/L placebo on 1st day and the reverse combination on a 2nd day. After training, patients underwent bilateral hand tapping at baseline and every 5 minutes for 60 minutes after dose ingestion. Stride length (SL) was recorded at 5-minute intervals with an ambulatory gait monitor. Patients identified their subjective latency to “on” and noted drug preferences and adverse events. They also underwent a UPDRS motor examination at baseline and 60 minutes after dose. Twenty subjects [15 male, age 68.7 (9.7), PD duration 13.4 (6.8)] completed. There were no significant group differences in tapping speed, subjective time to “on,” latency of increased SL, or overall preference. However, all trends did favor OD C/L. Adverse events were similar. This small pilot study did not show significant group differences favoring OD C/L; however, larger studies may be justified, and individual patients may benefit. © 2010 Movement Disorder Society

Key words: Parkinson’s disease; fluctuating; levodopa; orally dissolved levodopa; timed tapping; stride length

Parkinson’s disease (PD) is a common neurodegenerative disorder resulting in tremor, rigidity, bradykinesia, postural instability, and other motor and behavioral symptoms. Although initially satisfactory, continued treatment with carbidopa/levodopa (C/L) results in a reduced duration of response, dose failures, dyskinesia, and motor fluctuations within 5 years in the majority of patients.1,2 This occurs even more rapidly in younger patients.3 The etiology of these changes is probably multifactorial; however, inconsistent intestinal absorption of orally administered drug is felt to cause dose failures and dose inconsistencies.

A novel preparation of orally dissolving carbidopa/levodopa (OD C/L, Parcopa, UCB Pharma) has been introduced. A generic version is also available. This is not a true “sublingual” preparation, as it is absorbed lower in the gastrointestinal tract rather than through the oral mucosa. Pharmacokinetic studies found statistically similar results to regular oral C/L preparation, although OD C/L tended to have a shorter time to \( T_{\text{max}} \).4 Anecdotal evidence from our patient population suggested that some patients with fluctuating PD report a shorter duration to drug onset and a more consistent clinical effect with OD C/L, similar to that of C/L that is dissolved in liquids. One open-label report suggested...
that OD C/L was modestly preferred over oral CL/LD, but actual assessment measures were not different.5

PATIENTS AND METHODS

Subjects with fluctuating PD were recruited from the Baylor College of Medicine Movement Disorders Clinic. The protocol was approved by the Baylor College of Medicine IRB and registered at ClinicalTrials.gov. Inclusion criteria included: age 30 to 80, >3 year duration of PD symptoms, an “off” Unified Parkinson’s Disease Rating Scale (UPDRS) motor score of $\geq$25, and a history of fluctuations with C/L. The clinical study was a 2-day, single-dose, double-blind, double-dummy, crossover trial of oral C/L versus an identical dose of OD C/L.

Patients arrived in clinic in the A.M. in the practically defined “off” state. Subjects were randomly assigned to either OD C/L (Parcopa, UCB Pharma) or C/L (Sinemet, Dupont) at their usual morning dose (range 100–300 mg) if that dose normally caused problematic dyskinesia, or at the next highest dose that can be achieved in 50 mg increments if the initial dose did not usually cause dyskinesia. This was done to ensure that patients achieved an “on” state. A third person, not otherwise associated with the study performed the randomization (random number generator at our site) and administered the active drug and the placebo. Ten patients received OD C/L and 10 received oral C/L on the 1st day. Subjects first swallowed the oral C/L pill with water and then the OD C/L pill was placed in their mouth to dissolve on their tongue. The time from oral cavity placement to complete absorption was recorded. Then, they also took any other concurrent PD medications that they would normally take with their first dose. At the same time on the 2nd day, the active and placebo drugs were reversed and subjects underwent identical assessments.

Just before dosing, patients underwent the UPDRS motor section (part III) while “off.”6 Subjects who scored less than 25 on the motor examination were excluded. Patients were then trained with two iterations of a standard tapping speed test7 and a 10-m/180°-turn/10-m gait assessment. This took $\sim$10 minutes. Subjects wore a prototype ambulatory gait monitor consisting of triaxial angular rate sensors and triaxial accelerometers (SAGE-M, IM Systems, Baltimore, MD) to assess stride length (SL), speed, and variance. The gait monitor and its application to assessment of SL in response to medication administration in PD has been previously described in detail.8,9 After training, subjects performed two baseline tapping and two gait trials. The mean tapping response and SL of these two assessments were used as a baseline. Subjects were then administered the active drug and placebo and were assessed at 5-minute intervals for 60 minutes. Data collection was extended for a further 30 minutes if the patient did not feel that they were “on” at the end of the initial 60-minute period. A second UPDRS motor examination was assessed 60 minutes after drug ingestion. Subjective time to “on,” global impressions, and adverse events were collected.

The primary efficacy point was change in tapping frequency. Secondary efficacy points included time until SL increased 50% of the difference between baseline and maximum response, total change in SL over 60 minutes, time for “initial on” and “full on,” change in UPDRS motor scores, and overall drug preference.

Because of the delay in production of the prototype gait monitor and technical problems, SL data was not obtained on all subjects. The gait analysis only includes subjects with complete data from both days (N = 10).

It was reported by the randomizing coordinator that 1 subject swallowed the OD C/L dose on one of the days so the subject was excluded as a protocol violation and 1 additional subject was recruited so that 20 completed the study.

RESULTS

Twenty patients (15 male; 15 Caucasian, 3 Hispanic, 1 African, and 1 Asian) completed the study without protocol violation. The mean age was 68.7 (9.7) years and PD duration was 13.4 (6.8) years. All were fluctuating. The mean tested C/L dose was 190 (47.6) mg and the patient’s usual initial A.M. L-dopa dose was 152.5 (49.1) mg. As per protocol, 16 subjects took larger doses than their usual A.M. dose. The OD C/L usually dissolved rapidly, that is, 1.1 (0.8) minutes. Only 1 subject required more than 90 seconds for it to dissolve.

Tapping scores did not show any significant differences (Fig. 1A). Subjective time to initial “on” after ingestion was 22.1 (9.1) minutes with OD C/L vs. 26.2 (17.4) minutes with oral C/L (NS). Subjective time to full “on” was 33.9 (10.1) minutes with OD C/L vs. 38.4 (14.1) minutes with oral C/L (NS).

As expected in a fluctuating population, change in UPDRS part III scores was similar in both the groups: a 24.1 (8.1) improvement on OD C/L vs. 23.3 (7.8) on oral C/L. The baseline “off” UPDRS part III scores were also similar: 36.4 (8.2) OD C/L vs. 35.9 (8.1) oral C/L.
FIG. 1. A: Number of taps (mean and 95% CI) as a function of time since medication administration. B: Increase in stride length (cm) relative to baseline (mean and 95% CI) as a function of time since medication administration.
Gait analysis (N = 10) showed that SL increased to 50% of the difference between baseline and final values in 31.3 (12.0) minutes with OD C/L vs. 37.6 (19.1) minutes with oral C/L, NS. This calculated a time of 60 minutes for subjects whose SL did not increase significantly from baseline (i.e., above the mean + 1 SD of the baseline stride data) over the 60-minute epoch (1 patient with OD C/L and 3 patients with oral C/L). Mean SL at 60 minutes increased by 31.2 (21.7) cm relative to baseline with OD C/L vs. 21.8 (21.9) cm with oral C/L, a 34.5% increase relative to baseline with OD C/L vs. 25.2% (22.2) with oral C/L, (P = 0.1, two-tailed paired t-test).

Consistent with the tapping results (Fig. 1A), the mean increase in SL from baseline tended to be larger with OD C/L vs. oral C/L, particularly between 25- and 60-minute postadministration (Fig. 1B), although ANOVA revealed that this difference did not reach significance for any particular data point (the closest to significance being P = 0.06, 35 minutes after medication was taken). As a post hoc evaluation to increase the power of statistical comparison of the SL data was grouped into three bins, each spanning four data collection points; 5- to 20-minute, 25- to 40-minute, and 45- to 60-minute postmedication administration. The mean increase in SL from baseline was significantly greater (ANOVA) with OD C/L for all bins; 5 to 20 minutes, OD C/L 7.3 (13.6) cm vs. 2.1 (6.2) cm oral C/L (P = 0.044); 25 to 40 minutes, OD C/L 27.7 (25.1) cm vs. 13.5 (13.2) cm oral C/L (P = 0.044); and 45 to 60 minutes, OD C/L 38.1 (19.9) cm vs. 23.8 (18.1) cm oral C/L (P = 0.0029).

Overall 12 preferred OD C/L, six preferred oral C/L, and two felt they were identical. Adverse events reported only with OD C/L: dyskinesia (1). Adverse events reported only with oral C/L: nausea (2).

Interestingly, despite practice sessions, the 2-day baseline tapping scores 80.9 (26.5) tended to be more rapid than the day-1 baseline scores 69.0 (16.4), (P = 0.08). Yet by 45 minutes the tapping scores were identical, resulting in a more robust net improvement on day 1 for both drugs. Twelve subjects felt day 1 was “better,” whereas 6 subjects preferred the day 2 drug.

DISCUSSION

OD C/L did not show significant improvement over oral C/L in the primary (tapping) or secondary (gait analysis, UPDRS part III, subjective time to “on,” and global impressions) efficacy points. However, all assessments evaluating for duration to onset tended to favor the OD C/L preparation and more patients preferred it. Adverse events were similar.

Given our results, larger appropriately powered studies might show significant differences, although the effect size would likely be modest. As individual subjects often strongly preferred one or the other preparations, OD C/L could be considered on an individual basis, especially if the duration to onset is relatively prolonged with oral C/L preparations.

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Author Roles: William Ondo: study PI, study design, submission to ClinicalTrials.gov., obtained funding, manuscript writing, data collection, databasing, statistical analysis. Lina Shinawi: study coordinator, data collection, manuscript review. Steve Moore: developed gait accelerometer, manuscript review, statistical analysis.

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