Comparison of orally dissolving carbidopa/levodopa (Parcopa®) to conventional oral carbidopa/levodopa: A single dose, double-blind, double-dummy, placebo-controlled, cross-over trial

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ABSTRACT

Objective: To determine the latency to clinical onset of orally dissolving carbidopa/levodopa (C/L, Parcopa®) vs oral C/L in patients with fluctuating Parkinson's disease (PD).
Background: A single OD C/L preparation is available in the United States. This offers potential advantages to shorten the duration from ingestion to clinical onset. Surprisingly, this has never been clinically tested.
Methods: Patients with fluctuating PD and a UPDRS "off" motor score of >25 have been recruited for a two day, double blinded, single dose, cross-over study. Patients arrived in the morning in the practically defined "off" state and were randomized to receive either oral C/L and OD placebo or OD C/L and oral placebo, at identical doses on one day and the reverse combination on a second day. After training, patients underwent bilateral hand tapping at baseline (mean of 2 epochs) and every 5 minute for 60 minutes after dose ingestion. Stride length (SL) was recorded at 5 minute intervals with an ambulatory gait monitor. They also had a UPDRS motor examination at baseline and 60 minutes after dose. Patients identified their subjective latency to "on" and noted drug preference and adverse events.
Results: Fifteen subjects (11 male, age 67.7(10.0), duration of PD 13.9(7.9) have completed. There is no significant difference in change in UPDRS scores, subjective time to "on", improvement in tapping, or overall preference, although all trends favor OD C/L, and individual subjects demonstrated meaningful differences.
Conclusion: OD C/L may offer advantages in individual subjects but we failed to demonstrate significant group differences.

INTRODUCTION

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 five years in the majority of patients. [1,2] This occurs even more rapidly in younger patients. [3] The etiology of these changes is probably multi-factorial; however, inconsistent oral absorption is felt to be partially culpable.
A new preparation of orally dissolving carbidopa/levodopa (OD C/L, Parcopa®, UCB Pharma) has been introduced. This is not a true "sub-lingual" preparation as it is absorbed lower in the GI tract rather than through the oral mucosa. Pharmacokinetic studies found statistically similar results although OD C/L tended to have a shorter Tmax. [4] Anecdotal evidence from our patient population suggested that some fluctuating PD patients report a shorter duration to drug onset and a more consistent clinical effect with OD C/L, similar to that of LD dissolved in liquids. One open label report suggested that OD C/L was modestly preferred over oral CL/LD, but assessment measures were not different. [5]

METHODS

Twenty 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. Inclusion criteria included: age 30-80, a history of fluctuations and C/L use, >3 year duration of PD symptoms, an "off" UPDRS motor score of >25. The clinical study was a two day, single dose, outpatient, double-blind, double-dummy, cross-over trial of oral C/L vs. an identical dose of OD C/L.

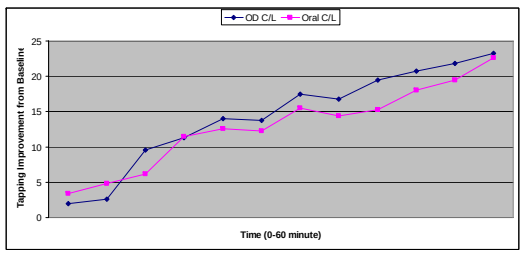
Patients arrived in clinic in the A.M in the practically defined "off" state. Subjects were randomized to either OD C/L or C/L (Sinemet®), at their usual morning dose (range 100 mg – 300 mg. LD) if that dose normally caused dyskinesia, or at the next highest dose that can be achieved in 50 mg increments if the initial dose did not usually cause dyskinesia. A third person, not otherwise associated with the study performed the randomization (random number generator) and administered the active drug and the placebo. They first swallowed the oral C/L then placed the OD C/L in their mouth. They then also took any other concurrent PD medications that they would normally take with their first dose. At the same time on the second day the active and placebo drugs were reversed and subjects underwent identical assessments.

Prior to dosing, patients underwent the Unified Parkinson's Disease Rating Scale (UPDRS) motor section (part III) while "off". [6] Subjects who scored less than 25 on the motor examination were excluded. They were trained with two iterations of a standard tapping speed test. [7] They also practiced a 10 meter/turn/10 meter gait assessment. Subjects wore a prototype accelerometer to assess stride length, speed, and variance. This is previously described in detail. [8] After training, subjects then underwent baseline tapping and walking assessments. They then took drug and placebo and were assessed at 5 minute intervals for 60 minutes (19 additional assessments). 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 time to change in change in tapping frequency. Secondary efficacy points included time to a 50% improvement in gait stride, change in UPDRS motor score, time to subjective "on", and clinical impressions.

RESULTS

Sixteen subjects have completed assessments. After all data collection, it was reported by the randomizing coordinator that one subject swallowed the OD C/L dose on the second day. They did not notice this so it was decided to exclude this subject if upon unblinding that dose was the OD C/L but enter them if it was regular C/L. It was OD C/L, so the subject was excluded from efficacy analysis.
Demographics: 11/15 males (12 Caucasion, 1 Hispanic, 1 African, 1 Asian), mean age 67.7(10.0), duration of PD 13.9(7.9).
The C/L dose was 197(48) mg. The OD C/L usually dissolved rapidly, 1.3(0.9) minutes. UPDRS part III scores improved by 25.0(8.9) on OD C/L versus 23.3(8.4) on oral C/L (NS). Subjective time to initial "on" was 23.9(9.9) minutes with OD C/L vs. 28.5(19.4) with oral C/L, (NS). Tapping scores did not show any dramatic differences but tended to be greater with OD C/L from 25-60 minutes. (Figure) Gait analysis is incomplete secondary to resolvable software issues. The mean time to a 50% increase in stride length was OD C/L 29(15) minutes vs. oral C/L 40(21) minutes, N=9. Overall 7 preferred OD C/L, 6 preferred oral C/L, and 2 felt they were identical. Interestingly, 10 preferred the drug they took on day 1, whereas only 3 preferred the drug on day 2.
Adverse events reported only with OD C/L were dyskinesia (1). Adverse events reported only with oral C/L included nausea (2).



CONCLUSIONS

OD C/L showed some trends toward more robust efficacy, however there were no significant group differences in any measured outcome. Recruitment is ongoing. Individual subjects often strongly preferred one or the other preparations. OD C/L should be considered on an individual bases.

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