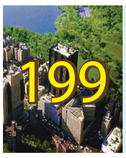

Gait analysis is more sensitive than finger tapping or UPDRS motor scores in assessment of the motor response to levodopa in Parkinson's disease

Steven T. Moore[1], Lina Shinawi[2] & William G. Ondo[2]

[1]Mt Sinai School of Medicine, New York, NY, USA; [2]Baylor College of Medicine, Houston TX.

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BACKGROUND

Levodopa use in fluctuating Parkinson's disease is complicated by an inconsistent and prolonged onset to clinical improvement. A single orally dissolved carbidopa/levodopa (OD C/L) preparation (Parcopa® UCBPharma) is available in the United States, which has the potential to shorten the duration from ingestion to clinical onset. OD C/L 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 to regular oral C/L preparation, although OD C/L tended to have a shorter time to Tmax. 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 C/L that is dissolved in liquids. The aim of this pilot study was to assess the relative time tio clinical onset of OD C/L and oral C/L.

METHODS

We tested 20 patients with fluctuating PD and a UPDRS "off" motor score of ≥25 in a two day, double blinded, double dummy, 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 (Sinemet®, Dupont) and OD placebo, or OD C/L and oral C/L placebo, at their usual morning dose (range 100 mg – 300 mg LD) on one day and the reverse combination on a second day. Patients were trained with two iterations of a standard tapping speed test and a 10 meter/180° turn/10 meter gait assessment. 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, speed, and variance (Moore et al. 2007, 2008a, 2008b). After training, patients perfromed the bilateral hand tapping and walking tasks at baseline and every 5 minute for 60 minutes after dose ingestion. Patients identified their subjective latency to "on" and noted drug preference 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) years, PD duration 13.4(6.8) years) completed the study.

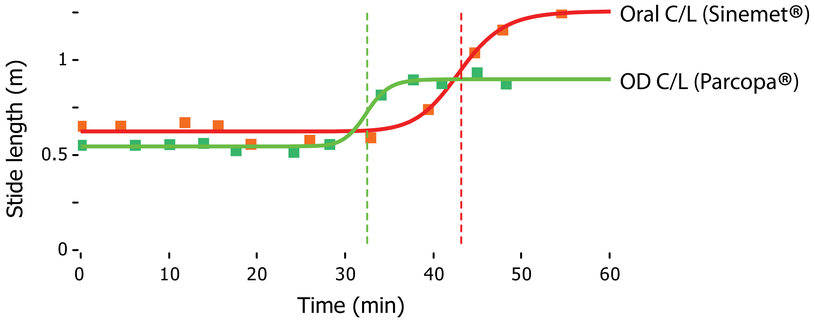

***Fig. 1**. Mean stride length data from a single subject following administration of equivalent doses of oral disintergrating C/L (green trace) and oral (red trace) C/L on consecutive days. Latency to drug effect was defined as the point where stride length increased 50% above baseline (dashed lines). In this subject latency was shorter with oral disintergrating C/L, but stride length in the 'on' state was larger with oral C/L.*

RESULTS

Tapping scores did not show any significant differences, but modestly tended to be greater with OD C/L from 25-60 minutes. (Fig. 2A) Subjective time to initial "on" was 22.1(9.1) minutes with OD C/L vs. 26.2(17.4) 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, improvement in UPDRS part III scores was similar in both groups: 24.1(8.1) 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.

Gait analysis (N=10) showed that stride length 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). Mean stride length 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%(28.9) 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. 2A), the mean increase in stride length from baseline tended to be larger with OD C/L vs oral C/L, particularly between 25-60 min post-administration (Fig. 2B), although ANOVA revealed that this difference did not reach significance (p=0.05) for any particular data point (the closest to significance being p=0.06, 35 min after medication was taken).To increase the power of statistical comparison the stride length data was grouped into 3 bins, each spanning four data collection points; 5-20 min, 25-40 min, and 45-60 min post medication administration. The mean increase in stride length from baseline was significantly greater (ANOVA) with OD C/L for all bins; 5-20 min, OD C/L 7.3(13.6) cm vs 2.1(6.2) cm oral C/L (p=0.044); 25-40 min, OD C/L 27.7(25.1) cm vs 13.5(13.2) cm oral C/L (p=0.044); and 45-60 min, OD C/L 38.1(19.9) cm vs 23.8(18.1) cm oral C/L (p=0.0029).

Overall 12 participants preferred OD C/L, 6 preferred oral C/L, and 2 felt they were identical.

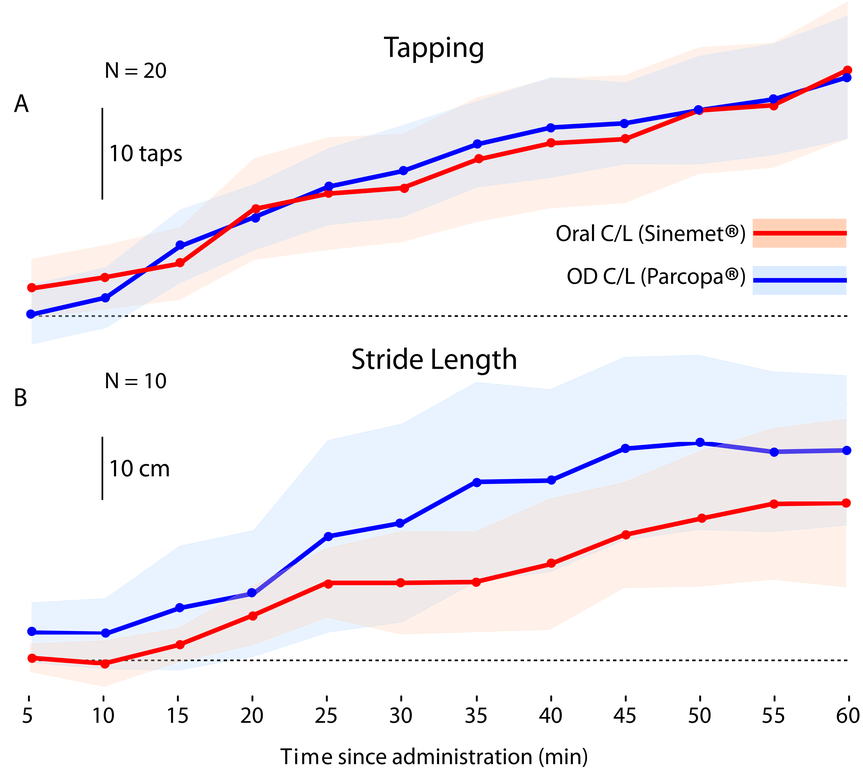

***Fig. 2A** Increase in number of bilateral finger taps (mean and 95%CI) relative to baseline as a function of time since medication administration. **B** Increase in stride length (cm) relative to baseline (mean and 95%CI) as a function of time since medication administration.*

CONCLUSION

Given our results, larger appropriately powered studies might show significant differences, although the effect would likely be modest. Since 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.

References

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