INTRODUCTION

Locomotor response to LD in fluctuating PD

The aim of this study was to quantify the dynamic response of locomotion to the first oral LD administration of the day in patients with fluctuating PD. Stride length was measured with an ambulatory gait monitor in 13 PD patients (8 males). Subjects arrived in the morning in an ‘off’ state and walked for a maximum length of 100 m. They then took their usual morning dose of oral LD and repeated the walking task at 13 min intervals (on average) over a 90 min period. Changes in stride length over time were fit with a Hill (Emax) function. Latency (time until stride length increased 15% of the difference between baseline and maximum response) and the Hill coefficient (shape of the ‘off-on’ transition) were determined from the fitted curve (Fig. 1).

Latency varied from 4.7 to 53.3 min post-LD administration (23.31 min [SD 14.9]), and was inversely correlated with age at onset of PD (R=0.83; p<0.0004) (Fig. 2a). Hill coefficient (H) ranged from a smooth hyperbolic curve (0.9) to an abrupt ‘off-on’ transition (16.9), with a mean of 8.1 (SD 4.9). H correlated with age at onset of PD (R=0.83; p=0.0004) (Fig. 3a). Hill coefficient H reflected both the sharpness of the transition from ‘off’ to ‘on’ (H coefficient) and latency. Hill function (curve fit)


time

LD + 16 min

LD + 55 min

Ambulatory monitoring of motor fluctuations and freezing of gait: objective assessment of pharmacological treatments in Parkinson’s disease

Ambulatory monitoring of FOG in PD

The power spectra of the freeze band (3-8 Hz) were not apparent during volitional standing. A freeze index (FI) was defined as the power in the ‘freeze’ band divided by the power in the ‘locomotor’ band (0.5 – 3 Hz), and a threshold determined such that above this limit were designated as FOG (Fig. 5). A global threshold detected 78% of FOG events, and 20% of stand events were incorrectly labeled as FOG. Individual calibration of the freeze threshold improved accuracy and sensitivity of the device to 89% (Fig. 6).

Ambulatory monitoring of freezing of gait

Freezing of gait (FOG) is common in advanced PD, is resistant to treatment, and negatively impacts clinical management of FOG.

Analysis of acceleration and angular velocity data of the leg provides the length of every stride taken over the recording epoch, and this information can be used to objectively assess improvements in locomotor function in response to LD. In addition, FOG episodes can be identified based on the appearance of high-frequency components of leg movement during FOG (subject 3-8 Hz) for a duration of up to 24 h. A clinical version of the SAGE monitor is being developed by IM Systems (Baltimore, MD) with funding from the NIH (PI Steven Moore).

Fig. 1. Patient stride length data following LD administration (at LD+0). Stride length was fit with a Hill function to determine the sharpness of the transition from ‘off’ to ‘on’ (H coefficient) and latency. Moore et al. (2007) Long-term monitoring of gait in Parkinson’s disease. Gait Posture 26: 200-207.

Fig. 2. Linear regression plots of latency vs age at onset of PD (a) and Hill coefficient (H) vs time since onset of PD (b). Moore et al. (2007) Long-term monitoring of gait in Parkinson’s disease. Gait Posture 26: 200-207.

Fig. 3. Vertical linear acceleration (6 s of data) of the left shank in a patient with advanced PD (top row) and power spectra of gait acceleration (bottom row). Note the appearance of high-frequency components (2.8 Hz) during freezng. Freezing of gait (FOG) is common in advanced PD, is resistant to treatment, and negatively impacts quality of life. In this study an ambulatory FOG monitor was validated in 11 PD patients. The vertical linear acceleration of the left shank was acquired using an ankle-mounted sensor array. Power analysis of the high-frequency range (2.8 Hz) showed freezing episodes in 44 FOG episodes from 7 patients (red trace) and from 46 periods (all 11 patients) of quiet standing (green trace). Moore et al. (2008) Ambulatory monitoring of freezing of gait in Parkinson’s disease. J Neurol Neurosurg Psychiatry 79: 369-376.

Fig. 4. Power spectra (mean and SEM) of gait acceleration of 44 FOG events from 7 patients (red trace) and from 46 periods (all 11 patients) of quiet standing (green trace). Support provided by NIH/NINDS 1R41NS059086-01 (Dr. Steven Moore).

Fig. 5. FOG detection algorithm. (a) Path taken by the subject 10 min post LD administration. This subject had 4 FOG events, initiating gait, at each 180° turn in the corridor, and when negotiating an obstacle. (b) Vertical linear acceleration of the left shank during the trial shown in (a). Red bars above the data indicate freezing episodes as determined from video recordings. (c) The freeze index (FI: freeze/red trace) was calculated from the power in the freeze band (3-8 Hz) divided by the power in the locomotor band (0.5 – 3 Hz). Large peaks are occurred during FOG. A freeze threshold could distinguish between FOG and periods of standing. Moore et al. (2008) Ambulatory monitoring of freezing of gait in Parkinson’s disease. J Neurol Neurosurg Psychiatry 79: 369-376.

Latency of orally disintegrating versus oral LD

Oral disintegrating (OD) LD offers potential advantages to shorten the duration from ingestion to clinical onset. Surprisingly, this has never been clinically tested. Patients with fluctuating PD and a UPDRS ‘off’ motor score of 25 were 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 (PO) LD and OD placebo or OD LD and PO placebo at identical dosages one day the other. The response analysis showed no differences between the two treatment periods. Patients underwent bilateral hand targeting at baseline and every 5 minute for 60 minutes after dose ingestion, and for 30 additional minutes if subjective ‘on’ was not achieved. Stride length was recorded in 10 min intervals with an ambulatory gait monitor and fitted with a Hill function. Subjects also had a UPDRS motor examination at baseline and 60 min. Patients identified their subjective latency to ‘on’ drug preference and vice-verses.

To date 12 subjects have completed the cross-over trial (8 male, mean age 68(10) years, duration of PD 16(8) years). Subjective latency was 26(9) minutes on OD vs. 32(10) minutes on PO. At 10 minutes PO the subjective latency was 25(10) minutes vs PO tapping improved by: (10 min) 4 vs. 14, (20 min) 14 vs. 33, (30 min) 19 vs. 13, (40 min) 20 vs. 13, (50 min) 21 vs. 16, (60 min) 25 vs. 21. The mean time to a 50% increase in stride length was OD 29(15) and PO 40(21) minutes. The off/ON UPDRS motor score improvement was OD 26(10) points vs. PO 12(12) points (p=0.03) for PO by 5. At this point trends suggest OD may have a quicker onset of action. Stride length measures were the most effective in discriminating differences in latency of OD and PO LD.