Many laboratory and clinical studies have demonstrated the ability of levodopa to increase stride length and walking speed, typically evaluating gait over short distances (<10 m) prior to administration (‘off’) of the levodopa medication cycle (see Morris (1) for review). However, the temporal dynamics of the locomotor response to levodopa, necessary for objective assessment of motor fluctuations, have not been successfully elucidated. A laboratory study (2) periodically assessed gait on a 7 m walkway over the levodopa dose cycle and found constant changes in stride length, likely due to the contrived nature of the laboratory walking task that can temporarily enhance performance in PD patients (3). In contrast, the fine-motor dynamic response to a standardized dose of levodopa (100 mg) has been assessed using finger-tapping at 15-min intervals post-administration (4). The drug effect-time curve (taps/min versus time-since-administration) followed a hyperbolic profile in early stages of the disease, with a sharper sigmoidal ‘off’-to-‘on’ transition in advanced PD. However, it is unclear whether finger-tapping accurately reflects the locomotor response to levodopa. A recent study has shown no correlation between the off-to-on transition and tapping and gait (5), suggesting a dissociation in the effects of levodopa on upper limb movements and locomotor function. In the current study we investigated whether a new ambulatory system for monitoring of gait (6) could be used to objectively assess locomotor fluctuations in PD.

**METHODS**

Participants diagnosed with idiopathic PD (8 males and 2 females) were enrolled in this study (Table 1). Age ranged from 45 to 72 years (62.3 [SD 9.2]) at onset of PD from 20 to 60 years (43.2 [SD 11.4]), and time since onset from 6 to 28 years (19.1 [SD 8.0]). All participants were prescribed oral levodopa as the primary component of their pharmacological management of PD, and had a clinical history of motor fluctuations. Participants arrived 8:00 am at the Movement Disorders clinic within the Department of Neurology at Baylor, without having taken their usual morning medication, in a clinically-defined ‘off’ state. Participants walked without assistance at a self-determined pace about a series of corridors of maximum length 100 m within the hospital complex immediately prior to usual morning dopaminergic medication administration (see Table 1). Participants repeated the walking task approximately every 15 min over a 90 min period post-administration. Distance walked was dependent on patient ability, ranging from 1 to 90 m (61 [SD 27]) when ‘off’ and from 30 to 94 m (80 [SD 21]) in the ‘on’ state. During the walking task the length of every stride was measured with an accuracy of 5 cm using a novel ambulatory device developed by the authors (6). An Inertial Unitless Measurement, 9° subject and Bluetooth serial transmitter were mounted around the shrank (just above the ankle) using an elastized strap and Velcro. The device weighed less than 130 grams and did not interfere with locomotion. Linear vertical acceleration and sagittal angular velocity of the leg were transmitted wirelessly to a Pocket PC carried by an investigator, who typically observed 3-4 meters behind the participant. After each walking trial leg movement data was processed using custom analysis software to provide stride length (6).

A drug-effect-time curve for the locomotor response to levodopa was determined by fitting all stride length values for each participant (total number of strides ranged from 284 to 892, mean 431 [SD 111]) with a sigmoidal (Hill) function (4) using the Levenberg-Marquardt algorithm (8, 9). The latency of the locomotor response to levodopa was calculated as the time taken from administration until stride length increased 15% of the difference between baseline and maximum response following levodopa administration. The Hill coefficient and latency showed a significant inverse relationship with age at onset of PD from 20 to 60 years (43.2 SD 11.4), and time since onset ranged from 6 to 28 years (19.1 SD 8.0). All participants were prescribed oral levodopa as the primary component of their pharmacological management of PD, and had a clinical history of motor fluctuations. A novel result was the latency to drug effect, i.e., increased stride length, was inversely related to age at onset of PD. In addition, the Hill coefficient was correlated with latency; the longer the delay until stride length increase the sharper the abruptness of the stride length transition from ‘off’ to ‘on’, was also determined from the fit. A regression analysis was performed to determine the relationship of latency and the Hill coefficient to patient age, age at onset of PD, time since diagnosis, the morning and total daily levodopa dose, and changes in stride length (baseline, final, and delta). Correlations were considered significant p < 0.05.

**RESULTS**

**CONCLUSIONS**

Despite the relatively small sample size, we observed that the latency and the Hill coefficient were statistically significant relationships were observed (Table 2). The Hill coefficient was positively correlated with both time since diagnosis (p=0.031) and latency (p=0.037). Latency was strongly correlated with age at onset of PD (p=0.007). Patients with advanced PD were younger, and thus latency was also correlated with age (p=0.035) as patients with young onset tended to be the younger subjects, and vice versa. However, a multivariable regression analysis adjusting for age and age at onset as set as independent variables revealed that age at onset remained a significant predictor of latency (p=0.013) whereas age did not (p=0.80). Similarly, age at onset (p=0.077) in the relationship of latency to time since diagnosis. The Hill coefficient quantified the abruptness of the locomotor response to levodopa showed no evidence of a relationship to the younger subjects, and vice versa. However, a multivariable regression analysis adjusting for age and age at onset as set as independent variables revealed that age at onset remained a significant predictor of latency (p=0.013) whereas age did not (p=0.80). Similarly, age at onset (p=0.077) in the relationship of latency to time since diagnosis. The Hill coefficient quantified the abruptness of the locomotor response to levodopa showed no evidence of a relationship to the younger subjects, and vice versa. However, a multivariable regression analysis adjusting for age and age at onset as set as independent variables revealed that age at onset remained a significant predictor of latency (p=0.013) whereas age did not (p=0.80). Similarly, age at onset (p=0.077) in the relationship of latency to time since diagnosis. The Hill coefficient quantified the abruptness of the locomotor response to levodopa showed no evidence of a relationship to the younger subjects, and vice versa. However, a multivariable regression analysis adjusting for age and age at onset as set as independent variables revealed that age at onset remained a significant predictor of latency (p=0.013) whereas age did not (p=0.80). Similarly, age at onset (p=0.077) in the relationship of latency to time since diagnosis. The Hill coefficient quantified the abruptness of the locomotor response to levodopa showed no evidence of a relationship to the younger subjects, and vice versa.

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Consistent with previous studies of the dynamic response of finger-tapping to levodopa (4, 10), the locomotor transition from ‘off’ to ‘on’, represented by the Hill coefficient, was correlated with disease duration. A novel result was the latency to drug effect, i.e., increased stride length, was inversely related in this study of PD. In addition, the Hill coefficient was correlated with latency; the longer the delay until stride length increase the sharper the transition from ‘off’ to ‘on’.

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