ORIGINAL ARTICLE

Gait Analysis in Advanced Parkinson's Disease – Effect of Levodopa and Tolcapone

Din-E Shan, Shwn-Jen Lee, Ling-Yi Chao, and Shyh-Ing Yeh

ABSTRACT: ***Objective:*** To determine the therapeutic effect of levodopa/benserazide and tolcapone on gait in patients with advanced Parkinson's disease. ***Methods:*** Instrumental gait analysis was performed in 38 out of 40 patients with wearing-off phenomenon during a randomized, double-blind, placebo-controlled trial of tolcapone. ***Results:*** Gait analysis disclosed a significant improvement by levodopa/benserazide in walking speed, stride length and the range of motion of hip, knee and ankle joints. At the end of the study, both the UPDRS motor scores during off-period and the percentage of off time improved significantly using tolcapone. However, gait analysis could not confirm this improvement. With respect to levodopa/benserazide effect, the reduction in rigidity correlated with improved angular excursion of the ankle, whereas the decreased bradykinesia correlated with improved stride length and angular excursion of the hip and knee joints. ***Conclusion:*** The results of our gait analysis confirmed that in parkinsonian patients with fluctuating motor symptoms levodopa/benserazide, but not tolcapone, produced a substantial improvement.

RÉSUMÉ: Analyse de la démarche chez les patients en phase avancée de la maladie de Parkinson – Effet de la lévodopa et du tolcapone. ***Objectif:*** Le but de cette étude était de déterminer l'effet thérapeutique de la lévodopa/bensérazide et du tolcapone sur la démarche, chez les patients en phase avancée de la maladie de Parkinson. ***Méthodes:*** Une analyse instrumentale de la démarche a été réalisée chez 38 de 40 patients ayant un phénomène de détérioration de fin de dose pendant un essai randomisé, en double insu, contrôlé par placebo, du tolcapone. ***Résultats:*** L'analyse de la démarche a montré une amélioration significative pendant le traitement par la lévodopa/bensérazide de la vitesse de la marche, de la longueur des foulées et de l'amplitude des mouvements des articulations de la hanche, du genou et de la cheville. À la fin de l'étude, les scores moteurs UPDRS pendant la période "off" et le pourcentage de temps "off" ont été améliorés significativement par le tolcapone. Cependant, l'analyse de la démarche n'a pas pu confirmer cette amélioration. En ce qui concerne l'effet de la préparation lévodopa/bensérazide, la diminution de la rigidité était corrélée avec l'amélioration de l'excursion angulaire de la cheville, alors que la diminution de la bradykinésie était corrélée à une amélioration de la longueur des foulées et à l'excursion angulaire des articulations de la hanche et du genou. ***Conclusion:*** Les résultats de notre analyse de la démarche confirment que, chez les parkinsoniens qui ont des symptômes moteurs fluctuants, la lévodopa/bensérazide procure une amélioration importante, ce qui n'est pas observé avec le tolcapone.

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Gait disturbance is a major component determining the functional disability in parkinsonian patients. However, only a small portion of clinical rating scales measure gait disturbance semiquantitatively. In contrast, instrumental gait analysis can provide more detailed, objective, and quantitative data than visual inspection. The gait pattern in patients with idiopathic Parkinson's disease is characterized by a reduction of walking speed, a low cadence (steps per minute), an increased duration of double support phases, a reduced stride length, and a smaller amplitude of joint movements.[1,2] Treatment with levodopa increases stride length, swing velocity, and decreases double support time.[1,3-5] However, instrumental gait analysis has rarely been performed in patients with advanced Parkinson's disease complicated by motor fluctuations to assess levodopa effect.[1,6,7]

Motor disability in Parkinson's disease results from the loss of nigro-striatal dopaminergic neurons. The supply of a

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dopamine precursor, levodopa, remains the treatment of choice.[8] Levodopa is metabolized peripherally by aromatic amino acid decarboxylase and catechol-O-methyltransferase (COMT); this conversion reduces the amount of levodopa passing across the blood-brain barrier.[9] Using levodopa in combination with a peripheral aromatic amino acid decarboxylase inhibitor may reduce the dosage of levodopa by approximately 70%.[10] However, the short plasma elimination half-life of levodopa of approximately 1.5 hours remains unchanged. This short half-life of levodopa is at least partially responsible for the occurrence of motor fluctuations in patients with advanced Parkinson's disease.[8] The addition of a COMT inhibitor may provide additional benefit by further blocking the peripheral conversion of levodopa.

Tolcapone is a novel COMT inhibitor. It can increase the bioavailability of levodopa and result in a prolonged elimination half-life.[11,12] In several large clinical trials in parkinsonian patients, tolcapone can reduce daily "off" time by 9.8% to 48%.[13-17] The following gait analysis was conducted to determine the efficacy of levodopa/benserazide and tolcapone in treating parkinsonian patients with motor fluctuations.

PATIENTS AND METHODS

Study design

A randomized, double-blind, placebo-controlled trial of tolcapone was conducted at one center in Taiwan and involved 40 Chinese patients. The trial was conducted according to the Declaration of Helsinki and its amendments. Local ethics committee approval was obtained before the start of the study. All patients gave written informed consent to participate.

Eligible patients were at least 30 years of age, had two of the three cardinal features of Parkinson's disease (rigidity, resting tremor, bradykinesia) and were clinically diagnosed as having idiopathic Parkinson's disease. The patients had been treated with levodopa for at least one year, had shown a clear improvement in the parkinsonian features with levodopa, and had to have at least two predictable motor fluctuations. Patients with nonidiopathic parkinsonism and atypical features were excluded from the study.[18]

All patients were screened for eligibility within the four weeks before randomization. During this period, the dosages of their levodopa/benserazide and any other antiparkinsonian drugs were stabilized. In addition, their ability to complete an "on/off" self-rating diary was assured. Patients were required to provide ratings for the preceding 30-minute period during the waking hours. Mobility was rated as "on" (good to excellent mobility), "intermediate" (neither "on" nor "off"), or "off" (ranging from poor mobility to complete blockade).

After screening, on visit two, eligible patients were randomly chosen to receive either placebo or tolcapone 100 mg three times daily according to a predetermined sequence that was blind to both the investigator and the patients. On visit three, after three weeks' treatment of tolcapone, the dosage could be increased to 200 mg three times daily if further benefit might be expected. The dosage of levodopa/benserazide could be reduced after the first day of treatment if the patient developed adverse dopaminergic symptoms. All the patients were requested to come to the clinic in the morning of visit two and visit four, before and after six weeks'treatment of tolcapone, during the defined "off-period" when levodopa was discontinued for at least 12 hours.

Study assessments

The efficacy and tolerance to tolcapone were assessed by the same doctor on visit four, at the end of week six. For analytic efficiency, we compared the following parameters after the treatment of tolcapone or placebo with those of the pretreatment level: 1) the change in the percentage of "off" time as assessed by the patient's diary record on at least three typical days during the week before the last clinic visit; 2) the change in the Unified Parkinson's Disease Rating Scale (UPDRS)[19] subscale III (motor function) evaluated during the defined "off-period" when levodopa was discontinued for at least 12 hours; 3) the change in the total score of UPDRS subscale I to III evaluated during the "on-period" on the same day; 4) the change in the intake frequency and total daily dose of levodopa. Adverse effects were evaluated by spontaneous reports, by measuring vital signs (heart rate and blood pressure), and by checking 12-lead ECG and laboratory tests (hematology, clinical chemistry, and urine analysis) at visits.

Gait analyses

Gait analyses were assessed during both the defined "off-period" and the optimal "on-period" of visit two and visit four. Their first morning dose of levodopa/benserazide with or without the controlled-release formulation, ranging from 100/25 to 400/100 mg, had been individualized for each patient and given as usual to obtain an optimal "on" state. The gait laboratory was equipped with Vicon 370 Motion Analysis System (Oxford Metrics, England) using six cameras at a speed of 60 frames per second. The reflective markers were attached on 13 anatomical landmarks of the bilateral lower extremities to measure the range of motion and temporal-distance parameters during gait based on a modified version of the Newington model.[20,21] To eliminate the bias of gait data from gait freezing and from acceleration at initiation and deceleration at termination, data were obtained only from the mid-gait of each of the 10 to 15 walking trials over a seven-meter walkway and averaged. Patients were requested to walk unassisted in both "off" and "on" status but allowed to take a rest between trials. Each gait assessment was completed in approximately 30 minutes.

Statistical analyses

Analyses of gait efficiency were performed on all patients who completed the trial. Tolerance analyses were performed on all patients included in the intent-to-treat populations. "On/off" time, UPDRS scores, total daily levodopa dose, and number of daily levodopa doses were analyzed using Wilcoxon rank sum test with the significance level set *a priori* at $p \leq 0.05$. For assessing the effect of levodopa/benserazide, the six parameters of gait analysis during baseline assessment in both groups were collected together and analyzed using the Wilcoxon paired signed-ranks test with the significance level set *a priori* at $p \leq 0.01$. For assessing the effect of tolcapone between the two groups, the six parameters of gait were analyzed using Wilcoxon rank sum test with the significance level set *a priori* at $p \leq 0.01$. Correlation between gait parameters and the UPDRS scores was analyzed using the Spearman rank correlation test with the

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Table 1: Baseline demographic data and key characteristics of Parkinson's disease

	Placebo	Tolcapone
Patients (N)	20	20
Male:female ratio (%)	80:20	85:15
Age (years)	67 ± 7	67 ± 4
Duration of disease (years)	9.5 ± 3.2	10.7 ± 3.0
Duration of levodopa treatment (years)	7.7 ± 3.0	9.4 ± 2.9
Total daily levodopa dose (mg)	930.0 (131.6)	795.0 (71.3)
Daily levodopa intakes (N)	4.4 (0.3)	4.5 (0.3)
"Off" time (% of waking day)	38.3 ± 19.2	36.3 ± 15.9
UPDRS total score (on time)	41.1 ± 13.4	45.3 ± 11.1
UPDRS Subscale II (ADL)	14.9 ± 5.3	17.5 ± 5.7
UPDRS Subscale III (motor, on time)	22.6 ± 8.6	23.5 ± 7.1
UPDRS Subscale III (motor, off time)	34.9 ± 9.9	29.9 ± 9.7

Where applicable, data are means ± SD, except for levodopa dosage, in which case data are means (SEM).
UPDRS = Unified Parkinson's Disease Rating Scale.
ADL= activities of daily living.

Table 2: Efficacy data: change (Δ) from baseline to week six after treatment of tolcapone

	Placebo	Tolcapone
Δ Total daily levodopa dose (mg)	-15.0 (15.0)	-55.0 (35.1)
Δ Daily levodopa intakes (N)	0 (0)	-0.3 (0.2)
Δ "Off" time (% Baseline)	3.2 ± 80.7	-43.5 ± 42.8*
Δ UPDRS total score (on time, % Baseline)	-13.2 ± 16.0	-19.1 ± 15.7
Δ UPDRS Subscale II (ADL, % Baseline)	-14.7 ± 15.1	-20.3 ± 15.0
Δ UPDRS Subscale III (motor, on time, % Baseline)	-12.7 ± 21.2	-18.1 ± 20.9
Δ UPDRS Subscale III (motor, off time, % Baseline)	-14.6 ± 13.4	-26.3 ± 14.5*

Where applicable, data are means ± SD, except for levodopa dosage, in which case data are means (SEM).
UPDRS = Unified Parkinson's Disease Rating Scale.
ADL= activities of daily living.
*p<0.05 versus placebo.

significance level set *a priori* at p≤0.01. The incidence of adverse effects was analyzed using a Chi-square test with the significance level set *a priori* at p≤0.05.

Results

Demographics

Table 1 shows a summary of baseline demographics of all patients. There were no notable differences regarding age, sex, height, weight, duration of Parkinson's disease, duration of levodopa treatment, dosage and dosing frequency of levodopa, percentage of "off" time, and UPDRS scores between the two groups. After randomization, 20 patients received placebo, and 20 received 100 mg tolcapone tid. On visit three, the dosage was increased to 200 mg tid in 20 patients of the placebo group and in 15 patients of the tolcapone group. The remaining five patients in the tolcapone group still received 100 mg tid due to marked improvement of efficacy or worsening of dyskinesia. Of the 40 patients enrolled, all had assessments at baseline and at the end of week six.

Efficacy

Table 2 shows that, after six weeks' treatment, there was a mild but not significant improvement in the UPDRS total scores, activities of daily living scores and motor scores during the "on-period" in the tolcapone group (p>0.05). The UPDRS motor scores during the "off-period" improved significantly in the tolcapone group when compared with those in the placebo group

Table 3: Gait characteristics during baseline assessment

	Placebo (n=19)	Tolcapone (n=19)	Total (n=38)
Cadence/off (steps/min)	108.9 ± 27.6	111.4 ± 18.9	110.1 ± 23.4
Cadence/on (steps/min)	111.2 ± 11.3	120.1 ± 9.8	115.6 ± 11.3*
Speed/off (cm/sec)	66.4 ± 23.3	71.3 ± 17.8	68.8 ± 20.6
Speed/on (cm/sec)	92.2 ± 22.5	99.6 ± 15.0	95.9 ± 19.2*
Stride length/off (cm)	74.9 ± 23.1	77.5 ± 17.4	76.2 ± 20.2
Stride length/on (cm)	98.5 ± 17.5	100.0 ± 16.6	99.3 ± 16.9*
ROM of hip/off (degree)	31.9 ± 7.6	31.4 ± 5.6	31.6 ± 6.6
ROM of hip/on (degree)	39.1 ± 6.6	39.1 ± 5.7	39.1 ± 6.1*
ROM of knee/off (degree)	46.0 ± 8.5	45.5 ± 7.7	45.8 ± 8.0
ROM of knee/on (degree)	52.4 ± 8.3	51.8 ± 4.7	52.1 ± 6.6*
ROM of ankle/off (degree)	20.2 ± 5.4	19.4 ± 4.0	19.8 ± 4.7
ROM of ankle/on (degree)	24.7 ± 5.1	22.7 ± 3.5	23.7 ± 4.4*

Where applicable, data are means ± SD. ROM = Range of motion. *p<0.01 versus same parameter during off-period.

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Table 4: Percentage of change (Δ) in gait characteristics after treatment of tolcapone

	Placebo (n=19)	Tolcapone (n=19)
Δ Cadence/off (% Baseline)	4.9 ± 9.6	5.0 ± 13.5
Δ Cadence/on (% Baseline)	3.5 ± 5.2	-0.5 ± 5.6
Δ Speed/off (% Baseline)	20.3 ± 21.1	20.7 ± 35.7
Δ Speed/on (% Baseline)	9.5 ± 22.9	0.6 ± 10.8
Δ Stride length/off (% Baseline)	14.4 ± 15.5	14.7 ± 29.8
Δ Stride length/on (% Baseline)	5.3 ± 17.6	1.2 ± 8.3
Δ ROM of hip/off (% Baseline)	7.9 ± 12.7	12.9 ± 20.9
Δ ROM of hip/on (% Baseline)	2.2 ± 11.8	0.7 ± 6.9
Δ ROM of knee/off (% Baseline)	6.1 ± 6.6	6.5 ± 17.5
Δ ROM of knee/on (% Baseline)	1.6 ± 8.2	-1.1 ± 5.5
Δ ROM of ankle/off (% Baseline)	9.6 ± 14.3	11.2 ± 35.7
Δ ROM of ankle/on (% Baseline)	-3.4 ± 11.2	2.2 ± 15.2

Where applicable, data are means ± SD.
ROM = Range of motion.

(p<0.05). Patient's diaries further supported the effectiveness of tolcapone in reducing the percentage of "off" time, since the decrease was significantly different from placebo, favoring tolcapone (p<0.05).

Gait analyses

Table 3 shows all the gait parameters during baseline assessment. There were no differences in most gait parameters between the two subject groups except for cadence at the "on-period". As compared with the data from the "off-period", all the six parameters improved significantly by levodopa/benserazide. Table 4 shows that there was no significant change in all the gait parameters at the end of the tolcapone trial (Power=38.5% for n=38). Table 5 shows the correlation between the change in gait parameters and the change in UPDRS motor scores following levodopa/benserazide treatment in the 38 patients completing gait analysis during baseline assessment. The change in the scores of rigidity had a significant correlation with the change in the range of motion of ankle, whereas that of bradykinesia had a significant correlation with the changes in stride length and in the range of motion of hip and knee joints. The change in total motor scores had a significant correlation with the change in walking speed.

Tolerance

Tolcapone was generally well-tolerated. Many of the adverse events (dyskinesia, nausea, hallucination, muscle cramps) are known to occur with levodopa therapy. When combined with other antiparkinsonian medicine, tolcapone tended to produce more dyskinesia than placebo did (7 vs. 1 patient, p<0.05). Dyskinesia became less severe after the dosage of levodopa/benserazide was reduced in our patients. One patient with pre-existing ischemic heart disease had more frequent attacks of angina, which became less severe only after the dosage of tolcapone was cut down to 100 mg tid and may be related to its potentiation of the peripheral effects of catecholamine.[22] Tolcapone treatment was associated with raised aspartate and alanine aminotransferases in one patient who happened to be a carrier of hepatitis B virus, suggesting the vulnerability of such a patient. Elevated aspartate and alanine aminotransferases have been reported in a few patients receiving tolcapone, which is currently suspended in Europe due to this potential hepatotoxicity.[14-16,23]

Discussion

The results of the present study confirmed previous findings that tolcapone could reduce "off" time in parkinsonian patients exhibiting the "wearing-off" phenomenon.[11,13-16,24,25] In addition, we demonstrated that the UPDRS motor scores during the defined "off-period" also improved significantly. This prolonged effect in the improvement of "off" motor scores could partly result from the ability of tolcapone to prolong the elimination half-life of levodopa by approximately two fold and the suppression of 3-O-methyldopa production by approximately 15 hours.[12,26]

Table 5: Correlations between the change (Δ) following levodopa for gait parameters and rating scales (n=38)

	Δ Cadence	Δ Speed	Δ Stride length	Δ ROM of hip	Δ ROM of knee	Δ ROM of ankle
Δ Tremor	0.08	-0.17	-0.11	-0.13	-0.22	-0.07
Δ Rigidity	0.26	-0.12	-0.28	-0.23	-0.17	-0.46#
Δ Tapping	-0.34	-0.19	0.01	0.08	-0.02	0.02
Δ Arising	-0.21	-0.30	-0.13	-0.13	-0.32	-0.15
Δ Gait	-0.05	-0.18	-0.16	-0.06	-0.23	-0.26
Δ Bradykinesia	0.12	-0.40	-0.44#	-0.49#	-0.52##	-0.35
Δ Posture	-0.08	-0.25	-0.24	-0.16	-0.20	-0.11
Δ Stability	-0.11	-0.16	-0.10	-0.02	-0.07	-0.23
Δ Masked face	-0.17	-0.31	-0.24	-0.27	-0.32	-0.22
Δ Speech	-0.18	-0.22	-0.16	-0.21	-0.35	-0.24
Δ Total scores	-0.19	-0.42#	-0.31	-0.23	-0.40	-0.38

ROM = Range of motion. ## p<0.001, # p<0.01

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The results of our gait analysis revealed a prominent effect of levodopa/benserazide by increasing cadence, stride length, walking speed, and the range of motion of hip, knee and ankle joints.[1] Our correlation analysis demonstrated that the improvement in rigidity correlated with an improved range of motion of ankle joint and that the improvement in bradykinesia correlated with improvement in stride length and in the range of motion of hip and knee joints. In addition, the results of our study confirmed O'Sullivan's finding that there was a poor correlation between the change in limb tapping and the change in gait parameters.[7] This finding supported the hypothesis that dopaminergic effect on neurons controlling axial movements and gait might be different from its effect on neurons controlling movements of distal part of limbs.

Our results also demonstrated that among the several scores in UPDRS the score of bradykinesia had better correlation with the gait parameters than the score of gait. One possible explanation was that in assessing bradykinesia, patients with marked slowness and hesitancy resulted in a score of 4, while in assessing gait, patients with severe disturbance of gait resulted in a score of 3. Only patients who could not walk at all resulted in a score of 4 in the gait examination of UPDRS. Thus the most severe patients suitable for gait analysis may have a score of 4 in the part of bradykinesia and a score of 3 in the part of gait. This difference in the range of score implies that the score of bradykinesia may be more sensitive than the score of gait in assessing the improvement in walking.

Both our results of UPDRS assessment and the results of gait analyses could not demonstrate any additional benefit during the "on-period" in the tolcapone group. One reason may be that tolcapone does not increase the maximum plasma concentration (C-max) of levodopa, but rather prolongs its half-life. Thus the patients would be able to experience longer "on" time, but the benefit that they received from levodopa was already maximal, with or without tolcapone. This ceiling response to levodopa/benserazide could account for our finding that tolcapone provides no additional benefit during the "on-period".

In contrast, our gait analysis could neither demonstrate any additional benefit in walking during the "off-period" in the tolcapone group. Several factors may account for this discrepancy between the results of UPDRS and the results of gait analyses: the elimination of assessment on start hesitation or hesitation near target during gait analysis, the longer duration spent at gait analysis, the impact of levodopa-induced dyskinesia or dystonia on gait pattern, the small proportion of scores in the UPDRS on the assessment of gait and the small sample size in our study.

The slight difference in the change of cadence between the two groups after levodopa/benserazide or tolcapone treatment may be of no importance. Cadence is a parameter that is subject to greater variability from test to test.[7] In addition, parkinsonian gait could be characterized either by a reduction of cadence or by a shuffling gait with a high cadence for a given speed.[2] In the former group the improvement in walking might be associated with an increase of cadence, whereas in the latter with a decrease of cadence. Until we have collected enough patients to divide them into two groups, we do not consider cadence a reliable parameter indicating improvement. Indeed, the regulation of stride length appeared to be the fundamental problem underlying gait difficulty in parkinsonian patients while increase of cadence was considered a compensatory mechanism.[2]

Instrumental gait analysis provides a detailed and objective measurement of the therapeutic response in parkinsonian patients. The results of our gait analysis confirmed a prominent effect of levodopa/benserazide in parkinsonian patients with motor fluctuations. A similar extent of improvement in the two groups of patients showed a good intertrial reliability for gait measurement. In addition, we demonstrated a good correlation between the improvement of clinical rating scores, particularly in rigidity and in bradykinesia, and the improvement of gait parameters. Although clinical assessment demonstrated a significant improvement by tolcapone in the UPDRS motor scores during "off-period", our gait analysis could not confirm this improvement.

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