Effect of Levodopa on Orthostatic and Postprandial Hypotension in Elderly Parkinsonian Patients

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Background. This study describes orthostatic and postprandial hypotension in elderly parkinsonian patients and evaluates the effect of levodopa therapy on orthostatic and postprandial hypotension in these patients.

Methods. Seventeen elderly patients with a clinical diagnosis of Parkinson's disease or parkinsonism based on the U.K. Parkinson's Disease Society Brain Bank criteria (age range, 66–84 years) participated in the study. Blood pressure was continuously monitored during standardized standing and meal tests, after starting 125-mg b.i.d. doses of levodopa/benserazide (Madopar) or placebo, in a double-blind, randomized, cross-over design. Seventeen age- and sex-matched healthy subjects served as controls.

Results. Orthostatic hypotension was infrequently found in parkinsonian patients (13%) and healthy subjects (6%; $p = .58$, between groups), whereas postprandial hypotension was more frequent in parkinsonian patients (82%) than in healthy subjects (41%; $p < .05$, between groups). Doses of levodopa/benserazide, administered 2 times per day, did not result in significantly larger blood pressure decreases after standing or eating, or in higher frequencies of orthostatic or postprandial hypotension in the parkinsonian group. Postprandial hypotension was related to disease severity ($r = -.56$, $p < .05$).

Conclusions. Postprandial hypotension, but not orthostatic hypotension, was more common in elderly parkinsonian patients than in healthy subjects. Therapy with 125-mg b.i.d. doses of levodopa/benserazide did not significantly aggravate orthostatic or postprandial hypotension.

O RTHOSTATIC hypotension (OH) and postprandial hypotension (PPH), defined as decreases in systolic blood pressure (BP) of ≥20 mm Hg after standing or eating, respectively, can occur when cardiovascular compensatory mechanisms become impaired (e.g., with increasing age or with Parkinson's disease or parkinsonism) because of altered autonomic function (1–5). OH and PPH can cause dizziness, lightheadedness, weakness, blurred vision, falls, or loss of consciousness (2). OH is found in 11% to 25% and PPH in 40% to 54% of parkinsonian patients (4−7).

Antiparkinsonian medication can impair autonomic or cardiovascular compensatory mechanisms and thereby aggravate orthostatic and postprandial BP decreases (3,6,8,9). In the treatment of elderly parkinsonian patients, levodopa in combination with a peripheral decarboxylase inhibitor is the most frequently used medication (10,11). Although it is known that levodopa, whether or not in combination with a peripheral decarboxylase inhibitor, can worsen OH (3,12–14), the effect of levodopa on PPH in elderly patients is unknown. However, the risk of OH, PPH, and related symptoms underscores the importance of diagnosing and preventing these syndromes in elderly patients. We hypothesized that elderly parkinsonian patients, who are already at higher risk of OH and PPH than healthy elderly subjects, would show worse orthostatic and postprandial BP decreases during levodopa therapy. This hypothesis implicates careful evaluation and adjustment of a patient's car-

diovascular comedication in case of OH or PPH during levodopa therapy.

This study quantified systemic hemodynamic responses during standing and after eating for elderly parkinsonian patients and healthy elderly subjects. In addition, the effect of levodopa was examined for the elderly parkinsonian patients in a double-blind, randomized cross-over trial with levodopa/benserazide (Madopar) and placebo. We evaluated heart-rate (HR) responses to standing and a Valsalva's maneuver, and orthostatic BP responses as parameters of autonomic function.

METHODS

Subjects

Elderly patients with clinically diagnosed Parkinson's disease or parkinsonism were recruited from the clinic and outpatient clinic of the Department of Geriatric Medicine, University Medical Center Nijmegen, and the Department of Neurology, Rijnstate Hospital, Arnhem, in The Netherlands. Eligibility required a clinical diagnosis of Parkinson's disease or parkinsonism according to the U.K. Parkinson's Disease Society Brain Bank criteria (15), an indication for low-dose levodopa/benserazide therapy, an age of ≥65 years, and a Clinical Dementia Rating Scale score of ≤0.5 (16). Exclusion criteria were drug-induced parkinsonism, use of neuroleptic medications with the potential to

cause parkinsonism, use of high-dose antiparkinsonian medication, and diabetes mellitus. Since we considered it unethical to withdraw therapy for patients on high-dose antiparkinsonian therapy, our study comprised only elderly parkinsonian patients with an indication for levodopa therapy in a relatively low 125-mg b.i.d. dose (17). A sample size of 15 subjects was required to identify a difference in BP response of ≥ 10 mm Hg ($SD_{BP\ responses}$ = 10 mm Hg, power = 80%, significance level = 5%). We aimed to include a total of at least 17 participants in the study, to account for a 10% drop-out rate. All consecutive potential participants from our clinic and outpatient clinic were approached and informed about this investigation via a letter or consultation. We had to approach 50 patients during a period of 1.5 years to include the required number of participants. Many patients refused to participate because the study involved a period without effective pharmacological therapy. Seventeen patients (8 men, 9 women; mean age, 75.4 ± 1.5 years [mean ± SEM], age range 66–84 years) completed the meal tests; 15 patients also completed the standing tests. The 17 patients had idiopathic Parkinson's disease (n = 12) or parkinsonism (n = 5) for 3.1 ± 0.7 years. The latter group included a patient with symptoms suggestive of progressive supranuclear palsy and a patient with symptoms suggestive of multiple system atrophy. Nine subjects used low-dose antiparkinsonian medications such as amantadine (n = 3), biperideen (n = 1), selegiline (n = 2), or levodopa/carbidopa (n = 5). These medications were withdrawn for at least 1 week before entering the study. Eight subjects had not previously used any antiparkinsonian medication. Thirteen of these patients led an active and independent life, regularly performing physical exercise such as walking and cycling, but 4 patients needed help for daily care.

In addition, we included 17 age- and sex-matched healthy subjects (mean age, 74.3 ± 0.9 years). These subjects had a medical history free of cardiovascular, pulmonary, renal, endocrinological, and neurological disorders; did not use medications; and led an active and independent life. All were in good physical health and regularly performed physical exercise. All subjects had a normal, balanced diet without salt, carbohydrate, or fat restrictions. They gave their written informed consent to this study, and the investigation was approved by the ethics committees for research on human subjects of the University Medical Center Nijmegen and the Rijnstate Hospital in Arnhem, The Netherlands.

Instrumentation and Procedure

BP was measured beat to beat by an automatic Finapres® device (TNO-BMI, Amsterdam, The Netherlands), which can be reliably and reproducibly used to monitor BP changes continuously and noninvasively in elderly subjects (18,19). BP was measured at the middle finger of the non-dominant hand unless the dominant hand showed less tremor than the nondominant hand. The finger used was kept at heart level at all times. A height detector (Department of Biomedical Engineering, University Medical Center Nijmegen, The Netherlands), which compared finger level and heart level at the fourth intercostal space in midaxillar line, corrected the BP signal for small hydrostatic pressure artifacts according to the formula BP (mm Hg) = finger BP (mm Hg) + 74 (mm Hg/m) × height (m). The BP signal was recorded with a sample frequency of 100 Hz. Absolute changes in systolic BP (SBP), diastolic BP (DBP), HR, and stroke volume (SV) were calculated off-line from the finger arterial BP waveform by the FAST-mf system software program Modelflow (TNO-BMI, Amsterdam, The Netherlands) (20,21).

This study was designed as a double-blind, randomized, two-treatment cross-over trial, involving pharmacological therapy with levodopa/benserazide at doses of 62.5 mg b.i.d. and 125 mg b.i.d. for a 1-week period each, and a placebo b.i.d. for a 2-week period. Patients and investigators were blinded to the therapy by use of identical capsules for levodopa/benserazide and the placebo. Before the study, randomization was performed according to the balanced allocation method, incorporating sex, presence of comorbidity or use of comedication with cardiovascular effects, hypertension, and signs of autonomic dysfunction as dichotomous covariates (22). We used levodopa/benserazide because combinations of levodopa and a peripheral decarboxylase inhibitor are most frequently and successfully used in the treatment of elderly parkinsonian patients and geriatric textbooks advise them (17).

Standing and meal tests were performed 3 times: once before the start of the cross-over study, once after 2 weeks of levodopa/benserazide therapy, and once after 2 weeks of placebo. On the days of testing, the subjects arrived at the hospital in the morning after an overnight fast and withdrawal of all medication from midnight the previous night. The tests took place in a quiet room at an ambient room temperature of 21 to 24°C. During the cross-over study, the parkinsonian patients took their morning dose of levodopa/benserazide (125 mg) or placebo just before the start of the tests. After instrumentation and a rest period of 10 minutes in a sitting position, the subjects performed a Valsalva's maneuver in a sitting position by blowing into a mouthpiece attached to a manometer. The subjects were instructed to maintain an expiratory pressure of 40 mm Hg for 15 seconds. They breathed normally after the release. Valsalva's maneuver was repeated at least once after a rest period of at least 1 minute. After the Valsalva's maneuvers, the subjects assumed a supine position for at least 15 minutes, after which they stood up within 15 seconds and remained standing for 10 minutes. Subsequently, they again assumed a supine position for 15 minutes; ingested a standardized 292-kcal liquid meal served at room temperature (consisting of 100 ml of Nutrical® [Nutricia, Zoetermeer, The Netherlands] and 100 ml of lactose-free whole milk, and containing 65 g of carbohydrates, 2 g of fat, and 4 g of protein) within 10 minutes in a sitting position; they then resumed a supine position for 75 minutes after the start of the meal (2). Patients were asked about possible symptoms during standing and after the meal; the symptoms were noted and classified in a severity score from 0 to 4. A score of 0 represented no symptoms; a score of 1 represented tiredness or sleepiness; 2 represented dizziness, lightheadedness, or restlessness; 3 represented severe weakness, feeling unsteady, feeling miserable, nausea, or vision changes; and a score of 4 involved speaking disturbances, decline in the level of consciousness,

syncope, or falling. Finally, the parkinsonian state was evaluated by administration of the 14-item motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) form, which metrically established bradykinesia; gait disorder or postural reflex impairment, or both; rigidity; and tremor (23). Each item was assessed with a severity scale ranging from 0 to 4, and the maximum total severity score was 56. Movements were limited as far as possible during the tests.

Data Analysis and Statistics

Autonomic function was determined on the basis of HR variability during Valsalva's maneuver, and HR variability and BP changes during standing. The HR variability in the Valsalva tests was expressed as the ratio of the maximum tachycardia to the maximum bradycardia induced by the maneuver during the 30 seconds following the release of the strain (Valsalva ratio) (13). The highest Valsalva ratio was accepted. HR variability after standing was expressed as the ratio of the 30th and 15th interbeat intervals after standing (30/15 ratio) (3,13). The BP responses after standing were defined as the SBP and DBP changes in the first and third minute of standing versus baseline (3,13).

During the standing tests, 1-minute averages of changes in BP, HR, and SV were calculated. Baseline values were defined as the last 1-minute averages before the posture change from a supine to upright position. OH was defined as a drop in SBP of ≥20 mm Hg after at least 1 minute of standing, as recommended by the American Autonomic Society and American Academy of Neurology (24). During the meal tests, 5-minute averages of the variable changes were calculated and baseline values were defined as the last 5-minute average values before the meal ingestion. PPH was defined as a drop in SBP of ≥20 mm Hg within 75 minutes after the start of meal ingestion (2).

Because a treatment-by-period interaction was not found, the results in the parkinsonian patients are presented as the overall results after 1 week of medication withdrawal, the overall results after 2 weeks of placebo, and the overall results after 2 weeks of levodopa/benserazide therapy. Two-way repeated measures analysis of variance, with simple contrast versus baseline, was applied to examine the effect of time, group, time-by-group, levodopa/benserazide, and time-by-levodopa/benserazide interaction on the postural changes and postprandial changes during each test. In addition, single data were analyzed by unpaired *t* tests between groups and by paired *t* tests within the parkinsonian group; χ^2 tests were performed for frequencies. The dependence of average postural or postprandial changes in BP on baseline BP levels, the autonomic function determined by HR and BP parameters, and the stage and severity of parkinsonism was evaluated by Pearson correlation tests. Statistical analysis was performed with SPSS for Windows, version 10.0 (SPSS Inc, Chicago, IL). A *p* value of <.05 was taken as the level of significance. The results are expressed as mean ± *SEM*.

RESULTS

Subject Characteristics

Age and resting BP and HR levels were similar in the 17 healthy elderly subjects and the 17 elderly parkinsonian pa-

tients (Table 1). Nine parkinsonian patients were allocated to the group receiving first the levodopa/benserazide therapy followed by the placebo; 8 patients received first the placebo and then the levodopa/benserazide therapy. The subgroups did not differ significantly in age, sex, BP and HR level, cardiovascular comorbidity, use of medication with cardiovascular effects, Hoehn & Yahr stage, or UPDRS score. A significant treatment-by-period interaction, due to period or carry-over influences of levodopa/benserazide, was not found. Therefore, the results are presented as total-group means for both treatments. The UPDRS motor score for the parkinsonian group was 20.6 ± 3.1 after the week of medication withdrawal, 20.6 ± 3.2 after 2 weeks of placebo, and 17.9 ± 3.1 after 2 weeks of levodopa/benserazide (*p* < .05 vs baseline and placebo).

Postural Changes in Hemodynamics

Two parkinsonian patients were unable to stand up within 15 seconds and remain standing without help and without disturbing the BP measurements. Therefore, the standing test was performed for 15 parkinsonian patients and for 17 healthy subjects.

One healthy subject (6%) and two parkinsonian patients (13%) showed OH (*p* = .58, between groups). The maximum individual SBP decrease after at least 1 minute of standing was −7.9 ± 6.6 mm Hg for the parkinsonian patients and −0.2 ± 3.4 mm Hg for the healthy subjects (*p* = .28, between groups). The parkinsonian group showed a seemingly different initial response of SBP, HR, and SV, but the difference was only significant for HR (*p* < .05, time-by-group interaction; Figure 1). Nine patients had mild to severe symptoms during standing: 3 experienced dizziness or restlessness (score of 2); 4 felt weak, unsteady, or miserable, or had nausea or vision changes (score of 3); and 2 felt unable to stand or had a decline in the level of consciousness (score of 4). These 2 patients had to sit down after 4 and 6 minutes of standing, although OH was not present in one of them at that time. Only 2 healthy subjects had mild symptoms; they felt tired upon standing (score of 1). The symptom score was not significantly related to the BP changes for either group.

Table 1. Subject Characteristics and Autonomic Function

	Parkinsonian Patients (*n* = 17)	Healthy Subjects (*n* = 17)
Subject characteristics		
Gender, male/female	8/9	8/9
Age, y	75.4 ± 1.5	74.3 ± 0.9
Systolic blood pressure, mm Hg	151 ± 4	148 ± 3
Diastolic blood pressure, mm Hg	85 ± 2	83 ± 2
Heart rate, bpm	72 ± 2	68 ± 2
Duration of parkinsonism, y	3.1 ± 0.7	—
Hoehn & Yahr stage	2.6 ± 0.3	—
UPDRS motor score	20.6 ± 3.1	—
Variables of autonomic function		
Valsalva ratio	1.33 ± 0.06 (*n* = 12)	1.43 ± 0.04
30/15 ratio	1.02 ± 0.02 (*n* = 15)*	1.09 ± 0.02

Notes: Data are expressed as mean ± *SEM*. UPDRS = Unified Parkinson's Disease Rating Scale.

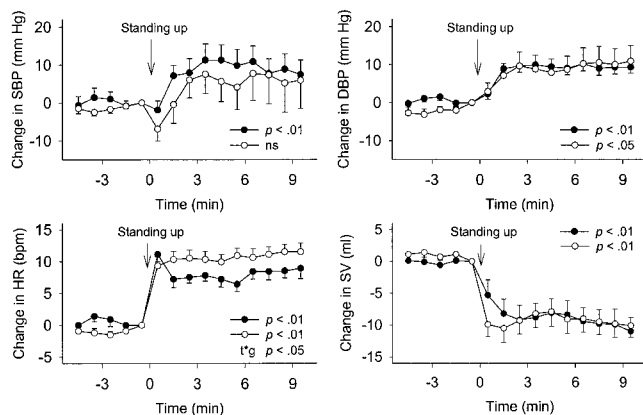*p < .05 vs healthy subjects (unpaired *t* test).

Figure 1. Orthostatic changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and stroke volume (SV) for elderly parkinsonian patients ($n = 15$; ○) and healthy elderly subjects ($n = 17$; ●). Values are expressed as mean $\pm$ *SEM*. The p values represent the time effect vs baseline, and the time-by-group interaction (t*g); group effects were not significant (NS).
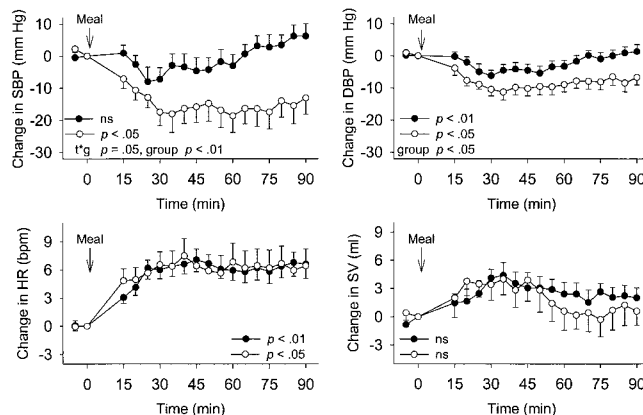

Figure 2. Postprandial changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and stroke volume (SV) for elderly parkinsonian patients ($n = 17$; ○) and healthy elderly subjects ($n = 17$; ●). Values are expressed as mean $\pm$ *SEM*. The p values represent the time effect vs baseline, the time-by-group interaction (t*g), and the group effect (group). NS = not significant.

During the cross-over trial in the parkinsonian patients, 4 patients (27%) showed OH during levodopa/benserazide therapy versus none during placebo. The maximum individual SBP decrease after at least 1 minute of standing was -0.1 ± 2.5 mm Hg during placebo and -3.2 ± 3.6 mm Hg during levodopa/benserazide therapy ($p = .07$, between tests). Particularly the decreases in SBP and SV seemed to be larger during levodopa/benserazide therapy (Table 2). However, a significant effect of levodopa/benserazide on the postural hemodynamic responses was not found during the 10-minute period.

A subanalysis, separating the patients in a group with idiopathic Parkinson's disease ($n = 11$) and a group with parkinsonism ($n = 4$), showed that the orthostatic BP responses were not different between these patient groups either before therapy or during the cross-over trial.

Postprandial Changes in Hemodynamics

Seven healthy subjects (41%) and 14 parkinsonian patients (82%) had PPH ($p < .05$, between groups). The maximum individual decrease in SBP was -33.8 ± 4.6 mm Hg for the parkinsonian patients and -15.8 ± 3.2 mm Hg for the healthy subjects ($p < .01$, between groups). Overall, SBP and DBP decreased significantly more ($p < .05$, between groups) in the parkinsonian group after the meal, whereas HR and SV showed similar postprandial changes in the two groups (Figure 2). Five parkinsonian patients felt tired or sleepy (score of 1); 2 experienced dizziness, lightheadedness, or restlessness (score of 2); 1 patient felt weak, miserable, and had vision changes (score of 3); and 1 patient started speaking indistinctly and had lowered consciousness (score of 4) after the meal. The symptoms score was related to the extent of the postprandial SBP decrease within the parkinsonian group ($r = -.67$, $p < .01$). None of the healthy subjects had any complaints, except for tiredness (score of 1, $n = 2$).

The postprandial responses of BP, HR, and SV, and the postprandial symptoms were similar in the parkinsonian patients after 2 weeks of placebo or levodopa/benserazide (Table 3). Eight patients (47%) showed PPH during placebo, and 10 patients (59%) showed PPH during levodopa/benserazide therapy. The maximum individual decrease in SBP was -26.0 ± 4.9 mm Hg during placebo and -22.4 ± 3.5 mm Hg during levodopa/benserazide therapy ($p = .38$,

Table 2. Postural Changes in Hemodynamics in Elderly Parkinsonian Patients ($n = 15$) During Placebo and During Levodopa/Benserazide Therapy (125 mg b.i.d.)

	First Minute		Third Minute	
Parameter	Placebo	Levo/bens	Placebo	Levo/bens
Systolic BP, mmHg	-0.9 ± 3.0	-6.4 ± 3.5	8.4 ± 2.4**	4.8 ± 3.4
Diastolic BP, mmHg	3.5 ± 1.8	3.1 ± 1.9	8.7 ± 1.9***	8.3 ± 2.5**
Heart rate, bpm	7.8 ± 1.2***	9.9 ± 1.8***	8.0 ± 1.0***	7.3 ± 1.6***
Stroke volume, ml	-6.0 ± 1.5**	-9.1 ± 3.1*	-6.6 ± 1.8**	-8.3 ± 2.9*

Notes: Data are presented as changes at the first and third min of active standing on both occasions and are expressed as mean $\pm$ *SEM*. Medication was taken approximately 30 minutes before standing. Levo/bens = levodopa/benserazide; BP = blood pressure.

*$p < .05$; **$p < .01$; ***$p < .001$, vs baseline (paired t test); the changes were not significantly different between the tests (paired t test).

Table 3. Postprandial Changes in Hemodynamics in Elderly Parkinsonian Patients During Placebo and During Levodopa/Benserazide Therapy (125 mg b.i.d.)

	30 minutes		60 minutes	
	Placebo	Levo/bens	Placebo	Levo/bens
Systolic BP, mm Hg	-16.2 ± 4.7**	-13.7 ± 3.8**	-8.3 ± 5.2	-8.6 ± 4.8
Diastolic BP, mm Hg	-11.5 ± 1.7***	-9.8 ± 2.4**	-6.6 ± 2.7*	-8.1 ± 2.3**
Heart rate, bpm	5.2 ± 1.3**	5.4 ± 1.4**	5.7 ± 1.7**	2.9 ± 1.3 *
Stroke volume, ml	4.1 ± 1.4*	3.6 ± 2.1	3.0 ± 1.7	4.1 ± 1.6 *

Notes: Data are presented as changes at 30 and 60 min after the start of the meal on both occasions and are expressed as mean $\pm$ *SEM*. Medication was taken approximately 60 minutes before eating. Levo/bens = levodopa/benserazide; BP = blood pressure.

*$p < .05$; **$p < .01$; ***$p < .001$, vs baseline (paired *t* test); the changes were not significantly different between the tests (paired *t* test).

between tests). Symptoms were noted by 8 patients (47%) during both tests. The postprandial BP decreases and the symptoms score were related during placebo (SBP, $r = -.41$, $p = .10$; DBP, $r = -.49$, $p < .05$) and levodopa/benserazide therapy (SBP, $r = -.50$, $p < .05$; DBP, $r = -.53$, $p < .05$).

A subanalysis, separating the patients into a group with idiopathic Parkinson's disease ($n = 12$) and a group with parkinsonism ($n = 5$), showed that the postprandial BP responses were similar in these patient groups before therapy and during the cross-over trial.

Autonomic Function

All healthy subjects performed standardized Valsalva's maneuvers of 35 to 40 mm Hg. Five parkinsonian patients were not able to perform reliable Valsalva's maneuvers because of functional restrictions, 3 patients were not able to produce an expiratory pressure exceeding 20 to 30 mm Hg, and 9 patients performed maneuvers of 30 to 40 mm Hg. The Valsalva ratio was not significantly lower for the parkinsonian patients than for the healthy subjects, but the 30/15 ratio was significantly lower ($p < .05$; Table 1). The orthostatic BP changes were not significantly different between the two groups. None of the autonomic function variables changed under low-dose levodopa/benserazide for the parkinsonian group (data not shown).

Correlations

Of the 15 parkinsonian patients who completed the standing and meal tests, 2 had both OH and PPH, 10 had only PPH, and none had only OH after 1 week of medication withdrawal. Of the healthy subjects, none had both OH and PPH, 7 had only PPH, and 1 had only OH. The frequencies of the two phenomena were not related to each other. However, significant relations were found between the individual orthostatic and postprandial BP decreases ($r = .52$, $p < .05$) and symptom scores ($r = .66$, $p < .01$) in the parkinsonian patients.

Postural changes in SBP were related to baseline DBP levels ($r = -.56$, $p < .05$) for the parkinsonian patients, but not for the healthy subjects. Relations between postural BP changes and age, autonomic function variables, or stage or severity of parkinsonism were not found.

Postprandial BP changes were not significantly related to baseline BP levels nor to autonomic function variables for either group, although the relation between the postprandial SBP change and the Valsalva ratio tended to be significant for the parkinsonian group ($r = .53$, $p = .07$). The postprandial changes in SBP and DBP were related to age ($r = -.53$, $p < .05$, both), and postprandial SBP changes were related to the Hoehn & Yahr stage ($r = -.52$, $p < .05$) and UPDRS motor score ($r = -.56$, $p < .05$) for the parkinsonian group.

DISCUSSION

The main findings of this study are twofold. First, the frequency of PPH was higher in elderly patients with mild to moderate parkinsonism than in healthy elderly subjects (82% vs 41%, $p < .05$), but the frequency of OH was not different between the two groups (13% vs 6%, $p = .58$). The postprandial BP decreases were related to the severity of parkinsonism and to postprandial symptoms in the parkinsonian patients. Second, therapy with the 125-mg b.i.d. dose of levodopa/benserazide did not worsen the orthostatic and postprandial hemodynamic responses, although the initial SBP decrease after standing seemed to be larger during levodopa/benserazide therapy.

The risk of OH, PPH, and associated cerebral symptoms increases with advancing age or diminishing autonomic function (1,2,25). The elderly patients with mild to moderate parkinsonism experienced PPH more often than the healthy elderly subjects. Remarkably, the frequency of OH was low in both groups. This discrepancy in occurrence of OH and PPH is in agreement with previous findings (4–6,26,27) and may result from different etiologies of OH and PPH (27). PPH might disclose a merely local or early impairment of autonomic regulation, especially of gastrointestinal perfusion, whereas OH might follow from more extensive and later-stage autonomic dysfunction (6). The individual orthostatic and postprandial BP changes showed a weak relation in the parkinsonian patients.

Levodopa has been reported to exert central hypotensive effects (3,13,28), impairment of the renin-aldosterone system (12), and hamper the efficiency of reflex vasoconstriction in an upright position, possibly as a result of depletion of the peripheral norepinephrine pool through continuous dopamine-mediated release (4,12). Other studies have reported that the OH effects of levodopa are limited (29,30). A 125-mg b.i.d. dose of levodopa/benserazide, which is often an acceptable dosage for elderly patients, did not signif-

icantly affect either orthostatic or postprandial BP changes, although SBP and SV seemed to decrease more after standing. A 125-mg b.i.d. dose of levodopa/benserazide is a relatively low dosage compared with dosages used in younger patients. When higher-dose therapy is indicated in elderly patients, careful orthostatic and postprandial BP monitoring may be advisable because hypotensive side effects may then become more pronounced.

Several explanations have been suggested for the etiology of OH or PPH in parkinsonian patients. Age-related factors, such as higher SBP levels, alterations in baroreflex-function, or lower HR, norepinephrine, and epinephrine responses are present; however, additional parasympathetic and sympathetic dysfunction, insufficient peripheral vasoconstriction, a lower dopamine excretion, and dopamine receptor supersensitivity resulting in more postprandial splanchnic vasodilatation can be involved as well (3–5,7,13,14,31,32). Autonomic dysfunction in patients with parkinsonism is generally mild, depending on the duration and severity of the disease, and occurs mainly in advanced cases (3,4,13,28–35). Parasympathetic dysfunction may be central rather than peripheral (34–35), whereas sympathetic dysfunction may involve insufficient peripheral vasoconstriction rather than central pathways (3,14,31,32). Our parkinsonian patients had no severe cardiovascular autonomic dysfunction, but merely a reduced 30/15 ratio, without a clear relation to the BP responses (13,29,30). The orthostatic BP responses were associated with higher baseline BP levels, whereas the postprandial BP responses were related to higher Hoehn & Yahr stages and UPDRS motor scores.

This study has several limitations. First, our study group was not uniform because we included patients with idiopathic Parkinson's disease as well as patients with parkinsonism, who did not meet the criteria for idiopathic Parkinson's disease but who did have an indication for low-dose levodopa therapy. Diagnostic accuracy for Parkinson's disease is poor in older patients, and Parkinson's disease is often considered as a syndrome that includes several diseases, such as idiopathic Parkinson's disease, multiple system atrophy, cortical Lewy body disease, and progressive nuclear palsy (17). A subanalysis revealed that the orthostatic and postprandial BP responses were similar in the patients with idiopathic Parkinson's disease and the patients with parkinsonism. Second, this study does not completely rule out OH effects of levodopa/benserazide immediately after standing, because a subtle difference in initial BP response seemed to be present, compared with placebo. However, this study was designed to demonstrate differences of ≥10 mm Hg, and the intraindividual variation in postural BP responses was large. Another limitation is that we only included elderly patients with mild to moderate parkinsonism who had an indication for relatively low-dose therapy with levodopa/benserazide. This study cannot be extrapolated to more severely affected parkinsonian patients or patients using higher doses of levodopa/benserazide. Finally, the substantial improvement in UPDRS score on levodopa/benserazide versus placebo could have influenced this double-blind study. However, we monitored BP fully automatically and the UPDRS score was evaluated after, not before, the BP measurements during each session.

In conclusion, PPH was present in 82% of the elderly patients with mild to moderate parkinsonism, whereas the frequency of OH was merely 13%. Therapy with 125-mg b.i.d. doses of levodopa/benserazide did not significantly aggravate the risk of OH and PPH. However, orthostatic and postprandial BP monitoring may be advisable when higher doses of levodopa therapy are needed in elderly patients.

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