Effects of Acute Levodopa Administration on Blood Pressure and Heart Variability in Never Treated Parkinsonians

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The effects of levodopa on autonomic nervous system (ANS) were investigated through the measurement of blood pressure (BP) and heart rate (HR) variability in 15 de novo parkinsonian who never received dopaminergic drugs. BP and HR were obtained using digital photoplethysmography in supine and standing positions. Measurements were achieved 90 min after administration, in a double blind cross-over way, of placebo or levodopa (200 mg) + benserazide (50 mg). Spectral analysis was performed using fast Fourier transformation (FFT) on 512 consecutive SBP and HR values. Spectral modulus was integrated for calculation of total spectra and of low frequency (LF: 66-129 mHz) or high frequency band (HF: respiratory frequency ± 50 mHz). After placebo, orthostatism was followed by a significant increase in BP and HR whereas relative variabilities in LF and HF remained unchanged. After levodopa, BP was significantly lower in supine position without changes in HR and LF. During orthostatism, changes observed in BP and in FFT were similar to those observed during placebo period. These data indicate that levodopa reduces supine and standing BP but does not impair orthostatic adaptation. This effect is not due to modification of BP or HR variability and appears to independent of any direct effect on ANS. (Hypertens Res 1995; 18 Suppl. I: 5175-5177)

Key Words: levodopa, autonomic nervous system, spectral variability, Parkinson’s disease

Several experimental studies have shown that anti-parkinsonian drugs affect cardiovascular regulation. Levodopa plus dopa-decarboxylase inhibitor, decreases blood pressure (BP) both in humans (1, 2) and in animals (3, 4) by acting at peripheral and/or central levels (5). Despite the large number of studies, no clear conclusions can be made concerning the effects of levodopa on autonomic nervous system (ANS). This is due to the heterogeneity of severity or duration of the disease which are correlated to the incidence of autonomic dysfunction (6, 7) but also to the lack of reliability of the methods used to investigate sympathetic or parasympathetic function.

Spectral analysis of BP and HR is a new simple technique to investigate ANS activity (8-10). Fast Fourier transformation (FFT) allows the identification of BP and HR oscillations occurring at 66-129 mHz or synchronous to respiration reflecting respectively sympathetic and parasympathetic activity.

In the present study, we investigated, in a double-blind cross-over way versus placebo, the effects of acute levodopa + carbidopa administration on BP and HR variability in supine position and after 15 min standing in 15 parkinsonian (PD) patients never previously treated with dopaminomimetic drugs.

Patients and Methods

Patients and BP and HR Measurements

Fifteen de novo PD patients (7 men and 8 women), mean age (61 ± 4 years), duration of disease (4 ± 1 years), Hoehn and Yahr stage 1 or 2, gave informed consent and were included in the study. They were all selected according to the UK brain bank criteria and had never been treated by dopaminergic drugs. None presented orthostatic hypotension or was taking drugs able to modify ANS activity. BP and HR were measured using digital photoplethysmography with Finapres®. The cuff was placed on the second phalang of the third finger of the dominant hand. A Dinamap was positioned on the opposite side in order to standardize the measures. Data form Finapres were digitalized at 500 Hz and stored. FFT was performed on series of 512 points on SBP and HR using Anapres software (Notocord systems, France). Energy of total spectrum and of 2 bands (LF: 70-130 mHz and HF: respiratory frequency ± 50 mHz) were calculated by integration of the spectral modulus.

General Procedure

Recordings were obtained at similar times on 2 consecutive days after a 30 min rest in supine position.
and after 15 min standing. Experiment begun 90 min after administration of placebo or Madopar (200 mg levodopa + 50 mg benzeraside). Drug sequences were randomised and double-blinded. The results are presented as mean values ± SE. Statistical analysis was performed using ANOVA followed by Fischer test. A p value <0.05 was considered as significant.

**Results**

**Blood Pressure and Heart Rate (Table 1)**

During placebo period, BP and HR significantly increased after 15 min standing. Forty-five min after levodopa, SBP was significantly lower in supine position without any change in MBP, DBP, or HR. Changes in BP and HR induced by standing up after levodopa did not differ from those observed after placebo.

**Spectral Analysis of SBP and HR (Table 2)**

After placebo, standing up was associated with a significant increase in energy of total spectrum and of LF band of SBP. No significant change was noticed on spectral parameters of HR. When considering the relative energy in the bands of interest, standing up did not induce noticeable change when compared to supine position.

After levodopa, in supine position, absolute and relative energies of the different spectral bands of SBP and HR were similar to those obtained with placebo. Standing up was associated with changes similar to those observed during placebo period.

**Discussion**

We selected only PD patients who never previously received antiparkinsonian drugs in order to really investigate the effects of acute levodopa administration. Several studies have investigated the effects of levodopa on cardiovascular responses. However, they were only performed in chronically treated patients deprived for some hours or their regular treatment (11-14). The dose administered was sufficient to induce motor effect in most patients but failed to induce symptomatic orthostatic hypotension (data not shown).

Levodopa reduced SBP in resting position and this was not associated with an increase in HR. The lack of tachycardia was previously reported and suggest that levodopa action on BP is from central origin (5). Despite its hypotensive action, levodopa does not impair cardiovascular adaptation to standing. This in accordance with results obtained in patients deprived of levodopa for 24 h. As previously reported (5) the sole effect of levodopa was a decrease of SBP which can be explained by its antiparkinsonian effects.

Spectral analysis is reproducible enough to allow to detect minimal changes in ANS in reduced
groups (15). Energy of LF band of SBP and HR is dependent of the activity of ANS and can be suppressed by alpha- and beta-antagonists (10). Energy of the HF band of HR is driven by the parasympathetic tone and abolished by muscarinic blockade (10). Standing is normally marked by an increase of BP and HR variability in LF range which correlates with an increase in catecholamine secretion and in sympathetic nerve activity. HR variability decreases as a consequence of reduced parasympathetic tone due to baroreflex desactivation. In our PD patients, FFT revealed that no clear change in LF can be detected after standing. Despite the absence of clinical evidence for autonomic failure this suggests that, even in the earliest stages of PD, ANS is not entirely intact. Such modifications cannot be detected by clinical reflexes but previous pharmacological studies performed by our group have shown alterations in alpha2-adrenoceptors in never treated patients (16). Levodopa failed to modify spectral parameters. This is unlikely to be due to limitations of the method or to a too small dose. Another explanation is that levodopa does not interfere with ANS activity but modifies BP through an action on central dopaminergic system involved in BP regulation.

In conclusion, these results suggest 1) the occurrence of autonomic dysfunction even in early stages of PD and 2) the effects of levodopa on BP do not depend on a direct effect on baroreflex mechanisms.

References