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Short report

Fluctuation of arterial blood pressure during end-of-dose akinesia in Parkinson's disease

M BARATTI, S CALZETTI

From the Istituto di Clinica Neurologica, Università di Parma, Parma, Italy

SUMMARY The supine and erect arterial blood pressure and pulse rate were measured in 13 patients with Parkinson's disease, chronically treated with levodopa and peripheral decarboxilase inhibitors presenting with or without On-Off phenomenon (end-of-dose akinesia). In the patients with dose-related response fluctuations the mean systo-diastolic blood pressure, both supine and erect, was found significantly higher during the Off phase as compared to the On phase and to that of the control group (patients with stable clinical response). The mean diurnal "excursion" of systo-diastolic supine and erect blood pressure in patients with On-Off phenomenon was significantly larger than in the control group. Although the clinical implications of such findings remain to be established, the results of this study indicate that arterial blood pressure fluctuations are a definite autonomic component of end-of-dose akinesia.

The wearing-off phenomenon (end-of-dose akinesia) is a biphasic fluctuation of motor performance occurring during long-term levodopa therapy in Parkinson's disease. Although motor disturbances are the most prominent and disabling clinical feature, autonomic dysfunction has also been reported in this condition. In particular, increase of arterial blood pressure has been described by Barbeau.[1] This study has been carried out in order to assess the degree of blood pressure fluctuations and the relationship between the blood pressure changes and the two clinical conditions of the phenomenon (phases with improved or reduced motility), which have not been previously reported.

Patients and methods

Thirteen patients with Parkinson's disease, chronically treated with levodopa plus peripheral decarboxylase inhibitors for at least 3 years, were included in the study. Seven of them presented with and six without end-of-dose akinesia. The latter were taken as controls. None of the patients had a history of cardiovascular, renal or other diseases, known to cause arterial hypertension. At the time of the study the patients were not taking any drugs other than those for Parkinsonism. The clinical features of the patients included in the study are summarised in table 1.

Systolic and diastolic blood pressure was measured in the right arm by using an aneroid sphygmomanometer, starting from the first morning dose of levodopa plus peripheral decarboxylase inhibitors (Madopar, Roche or Sinemet, MSD), at an interval of 2 hours for a total period of about 14 hours. Pulse rate was measured at the same time intervals. On each occasion, measurements of blood pressure and pulse rate were obtained after 10 min rest in the supine position and repeated after 3 min of standing. In the patients with end-of-dose deterioration the mean of three different measurements of blood pressure and pulse rate for each clinical condition (On and Off phases) was considered for analysis. The mean of seven different measurements of blood pressure and pulse rate was taken in the control patients.

Statistical analysis was performed by using Student's *t* test for unpaired data and parametric correlation coefficient (Pearson's r), to compute the relationship between the severity and the duration of the On-Off phenomenon and the degree of arterial blood pressure fluctuations.

Results

Table 2 shows the values of blood pressure and pulse rate in the patients studied. In the patients with daily fluctuations of motor performance the mean systolic and diastolic blood pressure, both

Address for reprint requests: Dr S Calzetti, Istituto di Clinica Neurologica, Università di Parma, Via del Quartiere 4, 43100 Parma, Italy.

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Table 1 *Clinical details of the patients with On-Off phenomenon and of the controls included in the study*

	On-Off patients	*Controls*
Age (yr) (mean ± SEM)	59·4 ± 3·0	63 ± 1·7
Sex	6 male 1 female	6 male
Duration of the disease (yr) (mean ± SEM)	13·3 ± 3·5	4·5 ± 0·4
Duration of On-Off phenomenon (yr) (mean ± SEM)	2·1 ± 0·5	—
Stage on Hoehn and Yahr's scale during Off phase	IV (3 pt) V (4 pt)	—
Dyskinesias during On phase	5/7	—
Duration of levodopa treatment (yr) (mean ± SEM)	6·4 ± 1·2	3·8 ± 0·4
Current levodopa therapy (mean daily dosage in mg)	593	450
Number of daily intakes of levodopa	3 (3 pts) 4 (3 pts) 5 (1 pt)	3
Other anti-Parkinson drugs	3/7 anticholin	2/6 anticholin

supine and erect, was found to be higher during the Off as compared to the On phase ($t = 2·79$, $p < 0·02$ for systolic and $t = 3·19$, $p < 0·01$ for diastolic in clinostasis; $t = 3·28$, $p < 0·01$ for systolic and $t = 2·65$, $p < 0·05$ for diastolic in orthostasis). The mean lying and standing pulse rate was similar during the two clinical phases.

In the On-Off patients, the mean values of systolic and diastolic blood pressure, both supine and erect, were higher than those of the controls during the Off but not during the On phase (supine: $t = 2·66$, $p < 0·05$ for systolic and $t = 3·17$, $p < 0·01$ for diastolic; erect: $t = 4·04$, $p < 0·01$ for systolic and $t = 3·22$, $p < 0·01$ for diastolic).

Compared to the controls, the mean pulse rate, both supine and erect, differed only during the On phase (supine: $t = 2·71$, $p < 0·02$; erect $t = 2·55$, $p < 0·05$).

When for each patient with the On-Off phenomenon the difference between the lowest and the highest value of both systolic and diastolic supine blood pressure ("excursion") was considered, only the mean excursion of the systolic was higher than that of the controls ($t = 2·39$, $p < 0·05$). On the contrary, on standing the excursion of both systolic and diastolic blood pressure were higher than those of the controls ($t = 2·64$, $p < 0·05$ for systolic and $t = 2·79$, $p < 0·02$ for diastolic). In any individual patient the highest and the lowest values of supine and erect systo-diastolic arterial blood pressure were invariably found during the Off and the On phases, respectively.

Neither in the patients with fluctuations of motor performance, both during On and Off periods, nor in the controls, was there any difference between the supine and erect systo-diastolic blood pressure and between supine and erect pulse rate. Only in one patient was there an orthostatic drop in blood pressure higher than 50 mm Hg for systolic and 30 mm Hg for diastolic, which occurred in both On and Off periods.

In the patients with end-of-dose akinesia the degree of arterial blood pressure fluctuations (taken as the excursion of both systolic and diastolic values) was neither correlated with the severity of the swings of motor performance (expressed according to the stage of Hoehn and Yahr's scale during the Off period) nor with their duration (expressed in years).

Table 2 *Mean values of supine and erect systo-diastolic blood pressure (mm Hg ± SEM), blood pressure excursion (mm Hg ± SEM) (see text for explanation) and pulse rate (beats/min ± SEM) in Parkinsonian patients with On-Off phenomenon and in the controls*

	On-Off patients			*Controls*
	On phase		*Off phase*	
Clinostasis				
Blood pressure (mm Hg)				
Systolic	130·5 ± 5·6		159·3 ± 8·7†§	132·5 ± 3·9
Diastolic	82·4 ± 2·2		97·8 ± 4·3‡¶	80·7 ± 2·9
Excursion				
systolic		55·0 ± 11·7§		24·2 ± 2·4
diastolic		32·8 ± 8·2		15·8 ± 0·8
Pulse rate (beats/min)	82·3 ± 4·8‖		78·3 ± 5·5	66·9 ± 2·4
Orthostasis				
Blood pressure (mm Hg)				
Systolic	123·1 ± 8·0		157·8 ± 5·8‡¶	127·0 ± 3·5
Diastolic	85·7 ± 5·7		102·8 ± 3·0*¶	88·5 ± 3·3
Excursion				
systolic		62·9 ± 11·2§		29·2 ± 3·9
diastolic		33·6 ± 6·3‖		13·3 ± 2·5
Pulse rate (beats/min)	91·9 ± 4·0§		87·4 ± 4·0	78·6 ± 3·0

*$p < 0·05$, †$p < 0·02$ and ‡$p < 0·01$ as compared to "ON" phase;
§$p < 0·05$, ‖$p < 0·02$ and ¶$p < 0·01$ as compared to controls.

Discussion

The wearing-off phenomenon is a dose-related response fluctuation of motor performance for which the pathophysiological mechanism has not been elucidated. Some believe that it is due to the progression of the disease with gradual loss of the ability of the brain to synthesise from its precursor amino-acids and store dopamine.[2] Others believe that it may be related to a reduced availability of brain dopamine, caused either by a competitive mechanism between levodopa and other dietary amino-acids (leucine, isoleucine and valine) for entry to the brain or to a change of pharmacokinetics of levodopa following its chronic administration.[3]

Although during end-of-dose deterioration autonomic disturbances frequently occur, only the relationship between respiratory dysfunction and the fluctuations of motor performance has been so far described in detail, to our knowledge.[4]

In our study it appears that a clear-cut relationship does exist for the blood pressure changes. This is supported by at least three observations: (1) the supine and erect systo-diastolic blood pressure was higher during the Off phase than during the On phase; (2) in any individual patient the lowest value of supine and erect systo-diastolic arterial blood pressure was invariably observed in the On phase, whereas the highest one always in the Off phase; (3) the mean "excursion" of supine and erect systo-diastolic blood pressure in On-Off patients was larger than that of the controls.

The lowering of supine blood pressure in patients with Parkinson's disease chronically treated with levodopa plus peripheral decarboxylase inhibitors is considered to be mediated at the CNS level but the exact mechanism has not been yet clearly established. The current hypothesis is that levodopa may interfere with the adrenergic transmission at the CNS synapses, as well as peripherally, "leading to impairment of proposed facilitatory nor-adrenergic systems in the hypothalamus or spinal cord".[5] The fact that in the patients with end-of-dose deterioration we studied both supine and erect blood pressure during On phase did not differ from the control patients and that it was found lower than during Off phase, suggests that a mechanism similar to the above may underlie, if any, the effect on blood pressure observed during the phase of improved motility.

On the other hand, it may be that in the Off phase the same mechanisms possibly involved in the pathogenesis of dose-related fluctuations of motor performance, leads indirectly to an increase in the synthesis and/or release of noradrenaline and ultimately to an increase of the systo-diastolic supine and erect BP.

Although the clinical implications of such findings remain to be established, the results of this study indicate that arterial blood pressure fluctuations are a main autonomic component of end-of-dose akinesia. Perspective follow-up studies on a larger number of patients are needed to confirm these data and to correlate the time-course of blood pressure fluctuations with the motor performance swings and other clinical variables.

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