Determinants of gait in the elderly Parkinsonian on maintenance levodopa/carbidopa therapy

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1 We have used gait analysis to investigate the efficacy of maintenance therapy with a levodopa/carbidopa combination in patients with idiopathic Parkinsonism, who do not have overt fluctuations in control in relation to administration of medication.

2 Fourteen patients (aged 64 to 88 years) receiving maintenance therapy with levodopa and carbidopa (Sinemet Plus) entered a placebo-controlled, randomised cross-over study of the effect of omission of a morning dose of active treatment on distance/time parameters of gait. Measurements made 2, 4 and 6 h after the morning treatment were standardised by taking the pre-treatment measurement on that day as baseline.

3 The mean increase in stride length (7%) and decrease in double support time (20%) on active treatment were small but statistically significant ($P < 0.0001$, in each case), there being no significant placebo effect on either gait parameter ($P = 0.69$ and 0.08 respectively). Neither active nor placebo treatments had any significant ($P > 0.45$ in each case) effect on the lying, standing or postural fall in mean arterial pressure, measurements being made in the same temporal relation to the treatments as was gait.

4 In a generalised linear model, after allowing for the effect ($P < 0.0001$) of intrinsic variability in pre-treatment speed as well as for structure of the study, nature of treatment had an effect on stride length over the whole walk, significant at $P = 0.002$.

5 Pre-treatment postural fall in mean arterial pressure was nearly as significant ($P = 0.003$) as the nature of treatment in the context of such a model: the greater the fall, the greater the increment in stride length seen following active or placebo treatment. This was probably explained by an acquired tolerance to the fall as the day progressed.

6 The major determinant ($P < 0.0001$) of the change in double support time over the whole walk, after allowing for the structure of the study, appeared to be the post treatment mean arterial standing blood pressure. The lower the pressure, the shorter the double support time, and hence, the greater the tendency to a hurried gait.

7 Nature of treatment, when added into the models described in summary points 5 and 6, had no significant effect ($P > 0.25$, in each case).

8 In elderly patients without overt fluctuations in performance in relation to medication, the effect of intrinsic variability in mean arterial pressure on gait, may confound the interpretation of an apparent treatment effect on stride length and, to an even greater extent, on double support time.

Keywords Parkinsonism levodopa carbidopa gait elderly

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Introduction

Many patients on maintenance levodopa therapy, in whom the diagnosis of idiopathic Parkinson's disease was made in their sixth decade or later, may not have overt fluctuations in control in relation to a given dose of the medication (Hildick-Smith, 1982), although the clinical state of that individual may vary from day to day. The objective assessment of benefit (Marsden & Schacter, 1981), once therapy has been started, is particularly problematical since unilateral involvement (with the normal side acting as running control) is not common. Moreover brady/hypokinesia and impaired balance tend to be their major disabilities, whilst the more readily quantified sign, tremor, may impair function little. Are, then, these patients being exposed to the risks of adverse reactions, such as postural hypotension and an increased incidence of falls, with no concomitant benefit?

In the present study the effect of omission of a morning dose is assessed by ability to walk: not only is walking important to the activities of daily living, but, also, timed tests correlate well with a 'global bradykinesia score' (Teräsväinen & Calne, 1980). A method of gait analysis suitable for use in clinic or ward has been adopted (Klenerman *et al.*, 1988). Of the three basic components of gait measured, length of stride and the hesitancy between swings (double support time), but not swing time, are selected for detailed analysis. Poverty of movement will reduce stride length and slowness will increase double support time. However, usually, hypo- and bradykinesia coexist and will have opposing effects on swing time.

A double-blind study of these distance/time parameters of gait was carried out on 4 days, 2 when the usual morning dose of a levodopa/carbidopa combination was given, the others when a placebo was substituted, in patients who exhibited no clinically overt fluctuation in relation to individual doses. An attempt was made to explain the changes in gait parameters observed in terms of nature of treatment, plasma concentrations of levodopa and its metabolite, 3-*O*-methyl dopa (3OMD), and the mean arterial blood pressure. The differential effects of these factors on the whole walk, the initial, often faltering, phase of walking and 'steady state' gait were considered.

Methods

Patients

Parkinsonism had been diagnosed initially by the presence of two or more of the four cardinal

signs, tremor, rigidity, bradykinesia and postural abnormality (either flexed posture or impaired postural reflexes). A history of improvement after levodopa therapy was regarded as essential to the diagnosis of idiopathic Parkinson's disease, although the amount of improvement required was not specified. Currently, any overt fluctuations in the patient's clinical state were not in temporal relation to individual doses. Alternate causes of Parkinsonism had been excluded according to a flow chart similar to that of Quinn & Hussain (1986). Patients in whom there were reservations about the diagnosis were excluded. Informed consent was sought from those eligible for the study, which had the approval of the local Ethics Committee.

Each patient had been established on the anti-Parkinsonian regimen of the levodopa (100 mg)/carbidopa (25 mg) combination, Sinemet Plus (Merck, Sharp and Dohme Ltd), alone, the last dose of the day (prescribed for 22.00 h) always being of two tablets. They were receiving no other anti-Parkinsonian agents.

Design of study

Patients were allocated randomly to receive a tablet of Sinemet Plus or an identical placebo at 10.00 h, with the alternate treatment at least 3 days later. Active and placebo treatments were then repeated after at least the same time interval had elapsed. Measurements of distance/time parameters of gait, over a maximum distance of 6 m, were carried out immediately before and at 2, 4 and 6 h after the 10.00 h doses on all 4 days. Treatments were repeated a second time, with measurement of supine (after 5 min) and erect (3 min) arterial blood pressure immediately before, and at 2 hourly intervals for 6 h after these latter two treatments. Samples of venous blood for assay of levodopa, and its metabolite, 3OMD were taken from an indwelling cannula immediately after each measurement of blood pressure. These procedures were carried out on separate occasions from the gait analysis in order to avoid the effects of fatigue on performance testing in a group of subjects, the majority of whom were frail.

A light, low protein breakfast was given one and a half hours before a 10.00 h treatment, no other food or drinks being allowed for a similar period of time after. No routine doses of Sinemet Plus were given after the 22.00 h dose on the night before, until 16.00 h on a treatment day, placebo tablets being substituted where appropriate.

Gait analysis

Distance/time parameters of gait were measured using the gait assessment trolley (Weller *et al.*, 1989). This method allows the patient to walk unhindered, using a walking aid if necessary. A 3 m length of strong cotton, clipped to the heels of the patient's shoes, passes around a pulley attached to a shaft encoder, which, in turn, is mounted on the lightweight trolley. When the patient walks, a length of cotton is transferred from behind one foot to behind the other. This causes rotation of the shaft encoder and tows the trolley along behind the patient. The length of cord transferred represents the distance moved and the direction of rotation of the encoder indicates which foot has moved. The trolley is designed to maintain tension in the cotton as the patient walks. A battery powered, infra red transmitter sends the encoded information to a receiver connected to a chart recorder. Gait on a given occasion (Figure 1) is represented by a single plot of distance against time, upward and downward deflections being proportional to distances moved by left and right foot respectively.

Biochemical methods

Venous blood samples were taken into heparin. Plasma was separated by centrifugation, and stored in aliquots of approximately 1 ml at -20°C until analysis.

Figure 1 Trace representing gait. Points A, C and E correspond to the left foot, the right and left again being lifted off the ground and B, D and F, to the left, right and left again striking the ground. A left step of length BG is followed by a right stride, HD, and then a left, IF. BC and DE are double support times, i.e., the time during which weight is borne on both feet between strides and velocity is zero. In the present work double support time was taken as being represented by the distance between points such as D and E, situated at a vertical distance of 1 mm from the maximum excursion of the stride HD.

Levodopa was separated from 3OMD by passing deproteinised plasma through phenylboronic acid (PBA) cassettes (Benedict & Risk, 1984). Levodopa was eluted from the PBA using perchloric acid (0.2 M) containing ethylenediamine-tetraacetic acid (0.25%). The eluates containing levodopa and those containing the 3OMD were analysed separately, using ion-pair, reversed-phase, high performance liquid chromatography with electrochemical detection.

Quantitation was achieved by calculation of the ratio of peak height to that of internal standards added to the plasma prior to extraction. The resultant peak height ratios were compared to a standard curve derived from spiked plasma, carried through the extraction procedure with the patient samples. The inter-assay coefficient of variation for levodopa was 7.4% at a concentration of 500 ng ml^{-1} , and for 3OMD was 2.5% at $3.0\text{ }\mu\text{g ml}^{-1}$.

Statistical analysis

Since the patients showed considerable variability in their gait between occasions, the gait parameters at 2, 4 and 6 h post-treatment were standardised by taking the pre-treatment measurement on the corresponding day as a baseline. Linear models were fitted to the gait data using the GLIM (1986) system. The following dependent variables were selected: (i) the change in mean stride length following treatment, and (ii) the change in mean double support time. The term mean was taken, in turn, to apply to the whole of each walk, to the first four strides of 'steady state' gait (as defined in Figure 2), and to the pre-steady state gait.

The formula for the base model, containing the structure of the study together with the grand

Figure 2 Definition used for 'steady state' gait. Lines WZ and XY were constructed by joining the points of initial contact of the right and left feet with the ground after the commencement of walking with a subsequent strike with the same foot, such that the lines did not cross any intervening part of the trace. The stride following the more distal point of contact (in this case, Z) between either line and the trace was taken as the first of steady state gait. Because of the short distance to be covered, steady state was taken to consist of only four consecutive strides and the corresponding four double support times.

mean was, in linear model notation (McCullagh & Nelder, 1983), $1 + S + O * T * E$, where 1 refers to the grand mean, S to the subjects, O to the order of treatments (active then placebo, or placebo then active), T to the time (2, 4 or 6 h after the baseline) when the observation was made and E to the exposure to the treatment (initial or repeat). S is regarded as a blocking factor, O a between subject factor, and T and E within subject factors.

This model was fitted to remove the effects of the structure of the study, and the residual sum of squares and degrees of freedom noted. Then an extra variable, such as baseline speed or nature of treatment (active or placebo), was added to the model, the new residual sum of squares and degrees of freedom noted, and the change in the residual sum of squares and degrees of freedom calculated. The mean square associated with adding that extra variable into the model was calculated from the change in the residual sum of squares divided by the change in the degrees of freedom. The residual mean square was calculated from the new residual sum of squares divided by the new residual degrees of freedom. The probability associated with the ratio of the mean square for that variable to the residual mean square, i.e. the *F* ratio, was used to assess the significance of the extra variable. If this probability was < 0.01 , the null hypothesis, that the extra variable had no significant effect on the variability of the dependent variable, was rejected. A significance level of 0.01 was adopted in order to reduce the chance of inclusion of 'nuisance' variables in the model, and to help identify only the more important variables.

This procedure was used in turn on all of the candidate variables, the one showing the greatest significance being incorporated into the model. The new model was then treated in the same manner as was the base model, the procedure being repeated for each remaining candidate variable. When no more variables achieved the level of significance required for incorporation into the model, the analysis was halted. In this final model, any component of the structure of the study of particular interest could be examined for significant effect on the gait variable.

The adequacy of the fit of the final model was assessed by residual analysis. The Shapiro Wilks W test (Royston, 1982) was used to test for normality and the Schweder (1981) test was used to see if the variances were the same in the order (O), time (T) and exposure to treatment (E) cross-classification. The change in gait was initially assessed by the post-treatment minus pre-treatment difference. However, if the residuals were not normally distributed and/or had differ-

ing variances, then the log of the post-treatment to pre-treatment ratio was considered as an alternative expression of the change. The expression showing least departure from the ideal was used in the model.

It was, of course, important to establish whether the nature of the treatment influenced the other candidate variables. Taking the change of the post treatment observations from the pre-treatment (baseline) value for each measure of plasma concentration and mean arterial blood pressure, in turn, as dependent variable, the model $1 + S + O * N$ was fitted, where S and O were defined as before and N was the nature of the treatment. (For each of these variables, since the observations were averaged over the 2, 4 and 6 h time points and the measurements had not been repeated on a further exposure to the treatment, the T and E terms of the base model were not relevant here.) The mean change for each variable could then be compared with zero by a two tailed, one sample, *t*-test using the mean square error from the model as the variance estimate.

In the results, where we wish to show the variability of values for a measurement from subject to subject, the range is quoted rather than the 95% confidence interval.

Results

Fourteen patients (aged 64 to 88 years) were studied. Three patients failed to complete the 6 m walk on at least one occasion, the minimum distance walked being 3 m. Their characteristics, daily maintenance dose of Sinemet Plus, plasma concentrations of levodopa and 3OMD and mean arterial blood pressure, in relation to treatment, are shown in Tables 1 and 2.

We examined whether any changes in plasma concentration of levodopa or 3OMD, or in mean arterial pressure accompanying treatment should be considered as independent of the nature of that treatment in assessing the prognostic factors for gait. Plasma levodopa concentration was, as expected, influenced by nature of treatment, there being a highly significant increase on active treatment ($P < 0.0001$) and no change at all after placebo ($P = 0.97$). There was still a small but significant ($P = 0.007$) decay in 3OMD over the 6 h following active treatment, but this was much less than the decay following placebo ($P < 0.0001$). Neither treatment had any significant effect on the lying or standing mean arterial pressure or its postural fall ($P > 0.45$, in each case).

The data on mean stride length and mean

Table 1 Characteristics of the 14 patients studied and their mean values for plasma levodopa concentration following active treatment

Patient	Age (years)	Height (cm)	Weight (kg)	Hoehn & Yahr staging	Duration of levodopa therapy (months)	Mean post- treatment levodopa** (ng ml ⁻¹)
1	81	148	54	5	78	168
2*	81	158	64	3	10	86
3	79	131	60	3	20	270
4	88	146	47	4	12	158
5*	80	187	62	4	107	95
6	76	157	58	2	95	125
7	77	154	52	4	100	84
8*	83	175	52	5	178	129
9	80	153	35	3	26	238
10	75	164	66	3	6	439
11*	75	171	73	3	11	629
12	74	157	71	4	22	296
13*	66	166	70	2	8	–
14*	64	179	67	2	36	169

* male

** mean of concentrations obtained for 2, 4 and 6 h post-treatment.

double support time, standardised according to pre-treatment values, are shown in Figure 3. The change in gait, expressed in terms of the mean for a measurement at each post-treatment session minus the mean pre-treatment value, gave homogeneous and normally distributed residuals in the case of swing length over the whole walk, and the pre-steady state and steady state parts of it. For double support time, a log transformation was necessary, the parameter being expressed as the difference between the logs of pre- and post-treatment values, that is the log of the ratio of post-treatment to pre-treatment value.

The *F* ratios produced when each of a series of variables was added separately to the base model for each dependent variable are compared in Table 3. For each dependent variable, there was a maximum of 168 observations. The residual degrees of freedom for the *F* ratios in the analysis of variance ranged from 108 to 128 for the whole and steady state gait and from 93 to 113 for the pre steady state gait. The value in a given case was calculated by subtracting from the actual number of observations (Figure 3), 24 for the structure of the study, one for each extra variable included in the model plus the number of missing observations. Where there was more than one extra variable included, the number of missing observations subtracted depended on how often the missing observations coincided. The degrees of freedom for the variable added into the model was always 1. It is interesting to

note that the timing of the post-treatment observation on gait (whether 2, 4 or 6 h) had no significant effect in any of the final models discussed below.

The overall mean for pre-treatment stride length was 49.2 (range 3.2 to 110.0) cm and the mean change 3.5 (95% C.I. 2.0 to 4.9) cm on an active treatment and 0.3 (95% C.I. –1 to 1.7) cm on placebo. That is the increment in stride length on active treatment was only seven per cent, on average, and there was no significant ($P = 0.69$) placebo effect.

When considering the whole walk, the pre-treatment free walking speed (overall mean 39.8, range 2.6 to 106.6, cm s⁻¹) appeared to have a more significant ($P < 0.0001$) effect on stride length, than did nature of treatment ($P = 0.004$) (Table 3a). As might be expected, the more closely the pre-treatment speed approximated to that observed in health, the less was the change in stride length seen accompanying (active or placebo) treatment: on average, for every 1 cm s⁻¹ by which the pre-treatment speed was higher, the change in stride length was 0.36 (95% C.I. 0.19 to 0.54) cm less. Allowing for the effects of speed as well as structure, nature of treatment had an effect on stride length of marginally greater significance ($P = 0.002$) than previously seen, but no additional effects of plasma concentration of parent drug or metabolite or of blood pressure could be detected.

Interestingly, the addition of pre-treatment

Table 2 Total daily maintenance of Sinemet Plus, the plasma 3-*O*-methyldopa concentrations and mean arterial blood pressure on active (A) and placebo (P) treatment days

Patient	Number of tablets/day*	Treatment	Plasma 3OMD concentration ($\mu\text{g ml}^{-1}$) in relation to treatment		Mean arterial blood pressure (mm Hg) in relation to treatment				postural fall before after	
			before	after**	lying before	after	standing before	after		
1	5	A	8.1	6.9	86	—	88	—	—2	—
		P	10.9	7.7	103	110	109	93	9	1
2	5	A	5.0	5.0	87	100	77	86	10	14
		P	2.7	2.4	97	93	85	84	12	9
3	5	A	7.5	6.2	144	130	126	136	18	—6
		P	7.8	5.6	124	152	132	143	—8	9
4	6	A	3.9	3.5	105	112	95	93	10	18
		P	—	3.4	127	128	113	116	13	13
5	8	A	6.5	6.1	120	116	101	102	19	14
		P	6.6	5.3	118	111	111	100	7	11
6	4	A	—	5.8	130	118	110	110	20	8
		P	4.9	4.3	142	114	141	107	1	8
7	5	A	5.2	5.5	108	97	97	92	11	4
		P	6.4	5.7	97	109	—	96	—	13
8	5	A	7.3	6.2	108	84	70	63	38	21
		P	8.1	7.3	71	93	57	90	14	3
9	6	A	2.5	3.1	122	135	125	124	—3	11
		P	3.0	2.3	114	122	112	123	3	—1
10	4	A	4.9	5.2	133	143	106	101	27	41
		P	5.3	4.4	140	134	131	100	7	34
11	4	A	3.0	2.8	98	94	96	86	2	8
		P	3.5	2.8	87	109	76	101	11	7
12	5	A	4.7	4.7	153	147	94	115	59	32
		P	5.4	4.3	120	103	120	102	0	1
13	4	A	—	—	113	105	104	88	9	18
		P	—	—	107	99	106	91	1	8
14	4	A	3.6	3.2	90	89	88	84	2	5
		P	3.2	2.8	71	85	77	87	—5	—2

* Maintenance dose of Sinemet Plus.

** Mean of values obtained for 2, 4 and 6 h post-treatment.

Figure 3 Effect of active (A) and placebo (P) treatments on gait, in individual patients (—) and averaged over the group (---) for the whole walk and the pre-steady state and steady state parts of that walk. a) For mean stride length the average value of the difference, post-treatment value minus pre-treatment value, for the three post-treatment sessions on the two exposures to a treatment in each patient, is shown. Of the possible 84 values (i.e. six per each of 14 patients) on each treatment, the missing data were as follows: for the whole and steady state gait, 8 on A, 7 on P; pre-steady state gait, 14 on A, 16 on P. b) For mean double support time the average value of the ratio of the post-treatment value to the pre-treatment, for the three post-treatment sessions on the two occasions in each patient, is shown. (The quantity and distribution of missing data on double support time was identical to that given above for stride length.)

postural fall in mean arterial blood pressure (overall mean 11, range -8 to 49 , mm Hg) to a model containing only the structure and baseline speed was nearly as significant ($P = 0.003$) as was the nature of treatment in this context. The greater the postural drop in the pre-treatment blood pressure, the greater the increment in swing length following treatment (active or placebo): a further drop of 10 mm Hg, for

example, foretelling an increment in stride length of 1.4 cm. No other variable added to this model reached significance at the 0.01 level.

When attention was focused on the pre-steady state part of the walk, neither baseline speed nor nature of treatment served as explanatory variables after adjustment for the structure (Table 3a). However, pre-treatment postural fall in mean arterial blood pressure just reached significance at the 0.01 level in this context, an increment in the drop foretelling, as above, an increment in stride length. Another measure of mean arterial pressure, the change in postural fall (overall mean 0, range -27 to 27 , mm Hg), had, by comparison, a highly significant ($P = 0.0006$) additional effect. However, in this case, an increment in the postural drop accompanying active or placebo treatment appeared to have a detrimental effect, a 10 mm Hg, increment being accompanied by a decrement in the change in stride length of 2.6 cm. After adjusting for structure and change in postural fall, no other extra variable had any significant effect.

The mean stride length in the steady state part of the gait appeared to be relatively uninfluenced by the extra variables: none was significant at the 0.01 level when added individually to the base model.

The overall mean reduction in double support time on active treatment was 20% (95% C.I. 15 to 25%) and on placebo was 6% (-1 to 12%). That is the excess decrement on active treatment was 14%, on average, and there was no significant ($P = 0.08$) placebo effect.

Table 3b shows the analysis of variance for mean double support time after taking account of the structure of the study. Considering the whole walk first, it can be seen that a number of variables, nature of treatment, post-treatment plasma levodopa concentration and several measures of mean arterial pressure, had a significant effect when added separately into this model. Active treatment caused more shortening of the double support time than did placebo, but the drug concentration ($P = 0.0006$) had only marginally greater significance in this context than did nature of treatment ($P = 0.0007$). (Had the post-treatment plasma levodopa concentration been measured more frequently, this variable may have attained even more significance.) Essentially, the tendency was that the lower the post-treatment lying and standing blood pressure and the smaller the change in these pressures from baseline, the greater was the shortening in double support time seen. The post-treatment standing blood pressure (overall mean 100, range 63 to 143, mm Hg) and the change accompanying treatment in lying pressure

Table 3 Results of model fitting for gait after taking account of structure of study

a) Mean stride length, expressed in terms of the difference of post-treatment values from the pre-treatment value

<i>Independent variables</i>	<i>F ratio</i> †		
	<i>Whole walk</i>	<i>Pre-steady state gait</i>	<i>Steady state gait</i>
Nature of treatment	8.49*	2.42	3.66
Pre-treatment speed	16.10***	0.40	0.60
<i>Plasma concentration</i>			
Post-treatment levodopa	3.23	0.48	1.86
Post-treatment 3OMD	0.05	0.00	0.01
Pre-treatment 3OMD	0.02	0.08	0.48
Change in 3OMD	0.00	0.10	0.84
<i>Mean arterial blood pressure</i>			
Post-treatment lying	0.26	0.32	0.95
Pre-treatment lying	5.46	2.19	0.10
Change lying	5.46	2.88	1.22
Post-treatment standing	1.17	0.10	1.27
Pre-treatment standing	4.78	4.43	5.59
Change standing	0.06	2.94	1.18
Post-treatment postural fall	3.37	0.22	0.13
Pre-treatment postural fall	6.60	6.71*	3.08
Change in postural fall	3.80	12.57**	4.58

b) Mean double support time, expressed in terms of the log of the ratio of post-treatment values to the pre-treatment value

<i>Independent variables</i>	<i>F ratio</i>		
	<i>Whole walk</i>	<i>Pre-steady state gait</i>	<i>Steady state gait</i>
Nature of treatment	12.06**	8.96*	0.85
Pre-treatment speed	0.42	2.40	0.03
<i>Plasma concentration</i>			
Post-treatment levodopa	12.33**	8.62*	3.51
Post-treatment 3OMD	2.59	1.58	0.24
Pre-treatment 3OMD	4.66	5.76	0.10
Change in 3OMD	0.24	2.46	0.16
<i>Mean arterial blood pressure</i>			
Post-treatment lying	14.55**	6.09	4.37
Pre-treatment lying	9.71*	6.01	0.63
Change lying	33.92***	19.26***	5.44
Post-treatment standing	30.40***	5.13	7.32*
Pre-treatment standing	3.79	0.16	0.45
Change standing	15.05**	0.40	3.31
Post-treatment postural fall	0.08	3.25	0.01
Pre-treatment postural fall	0.52	0.71	0.05
Change in postural fall	0.59	8.43*	0.01

† assessing significance of independent variables when fitted separately to the base model. (For degrees of freedom, see **Results**.)

* $P \leq 0.01$, ** $P \leq 0.001$, *** $P \leq 0.0001$.

(overall mean 0, range -28 to 28 mm Hg) had the most significant additional effects of the extra variables considered ($P < 0.0001$ in each case). A decrement in post-treatment standing blood pressure of 10 mm Hg, for example, appeared to be accompanied by a decrement of 28% in the ratio of post-treatment to pre-treatment double support time, whilst a decrement in the change in the lying pressure of the same magnitude was accompanied by a decrement of 13% in the ratio. However, after adding the post-treatment standing blood pressure to the base model, no other variable had any significant effect, but after adding the change in lying pressure, post-treatment standing pressure still had a marginally significant ($P = 0.016$) effect. Neither nature of treatment nor any other extra variables significantly improved either of these models.

The general trend, the lower the post treatment pressure and the smaller its change, the greater the shortening of the double support time, was echoed in the pre-steady state and steady state gait data. The extra variables which had the most significant effect on these two parts of the walk, respectively, were the change in pressure lying and post treatment standing pressure ($P < 0.0001$ and $P = 0.008$), shortenings of 15 and 18% in double support time corresponding to decrements of 10 mm Hg.

A decrement in the change in pressure (post-minus pre-treatment) can, of course, theoretically be achieved not only by a decrement in the post-treatment pressure, but also by an increment in the pre-treatment pressure. There was a tendency for an increment in pre-treatment pressure to result in shortening of the double support time. This reached significance at the 0.01 level when the effect of the extra variable, the pre-treatment lying blood pressure (overall mean 111, range 71 to 153 mm Hg), was considered on the data for the whole gait ($P = 0.002$). The magnitude of this effect was relatively small (an 8% decrement in duration for a 10 mm Hg increment in pressure).

Discussion

We (Leeman *et al.*, 1987) have previously reported on the response to night time dosing with a levodopa/carbidopa combination in a group of patients, with no marked fluctuations in control in relation to daytime medication, who had commenced levodopa therapy at between 68 and 87 years of age. An improvement was seen in sleep, and in time to walk an (individually) fixed distance on the morning following active treat-

ment. In a similar patient group, gait analysis appeared to allow a small effect of omission of a morning dose on stride length and on double support time to be detected, the effect on stride length being only slightly more prominent after correction for intrinsic variability in morning performance as measured by walking speed. No placebo effect was identified. However, use of generalised linear models to explain the variability in each of these two gait parameters over the whole walk, showed that the nature of the treatment had no significant effect on gait after incorporation of a measure of mean arterial pressure into each model. Moreover, pretreatment values and the changes observed in mean arterial pressure appeared to be independent of whether the treatment given was active or placebo. We conclude that, in such a population, the influence of blood pressure on gait is sufficiently strong to confound interpretation of small treatment effects on performance.

Further work is needed to determine whether omission of active treatment for 6 h is sufficiently long fully to estimate the efficacy of maintenance therapy in individual patients (Figure 4), particularly since any overnight sleep benefit may tend to mask the potential benefit of a morning dose. It may, indeed, be necessary to assess the effect of withdrawal of therapy after intervals of 24 h in such patients.

After correction for baseline speed, the mean increase in stride length following a morning treatment appeared to be greater, the greater the postural fall in mean arterial pressure before that treatment was given. Since there was no evidence that the postural fall lessened following either active or placebo treatment in the patient group as a whole, this was probably explained by an acquired tolerance to the fall as the day progressed. Such an acquired tolerance could, of course, tend to simulate a beneficial effect of that day's treatment.

Over the whole walk, the major determinant of the change in double support time seemed to be, not the nature of treatment, but the post-treatment mean arterial standing blood pressure. Having added this to the base model, neither any other pressure variable nor any treatment-related variable retained a previously significant effect on double support time. Moreover, the direction of this predominant effect was the lower the pressure, the greater the shortening in double support time. Presumably patients with postural instability adopted a hurried gait with a shorter double support time as well as (after the initial faltering phase of gait) a longer stride length. Thus changes in double support time attributable to an effect of blood pressure may simulate a

Figure 4 Hypothetical response/time profiles to levodopa maintenance therapy in Parkinson's disease. Unlike in figure a), our patient group showed a response to treatment, but follow-up for only 6 h and the possibility of confounding influences due to rest benefit and/or diurnal rhythm precluded distinction between b) where storage capacity in the presynaptic neurones is sufficient to produce a flat response curve, c) where storage capacity is limited and some fluctuation against a background of longer duration response is seen and d) where storage capacity is so reduced that only an effect of short duration is seen.

beneficial effect of treatment on gait. A genuine beneficial effect may be seen only when the pre-treatment blood pressure is sufficiently high to counteract any deleterious effect of treatment on pressure whilst walking (see below).

No effect of mean arterial blood pressure, baseline speed or nature of treatment was seen on stride length during the steady-state part of the short walk. The main impact of these variables was during the initial phase of gait and perhaps during the inhibition caused by approaching a wall at the end of the whole walk, rather than on that part of the whole walk where, by definition, peak stride length was likely to have been achieved. Indeed, during the initial phase of the walk, the greater the actual increment or decrement from baseline in postural drop, the greater or lesser, respectively, became the difficulty experienced by patients in stepping

out. Thus overnight exposure to the baroreceptor stimulus of a head up tilt may help those with a postural drop and an initial faltering phase to gait (Bannister *et al.*, 1969).

It is of clinical interest to note that an increment in the postural drop following treatment was associated with not only more difficulty stepping out but also greater hesitancy between steps during the initial phase of gait. In other words, postural instability may have manifested itself in an initial, hesitant 'marche à petits pas' (see Figure 2).

Autonomic dysfunction occurs in association with untreated Parkinsonism (Appenzeller & Goss, 1971; Parkinson, 1955). According to the diagnostic flow chart used (Quinn & Husain, 1986), it is not an exclusion criterion for the diagnosis of idiopathic Parkinson's disease, but multiple system atrophy is. Moreover, it is often assumed that the blood pressure in idiopathic Parkinson's disease is lower than that expected on the grounds of age. However, Aminoff *et al.* (1975) found 'casual' blood pressure in 141 Parkinsonian subjects not to be significantly different from that of matched controls. Gross *et al.* (1972), using intra-arterial recording, were able to show a greater fall in blood pressure in response to tilt in Parkinsonian patients than in age-matched controls, but similar responses to the Valsalva manoeuvre. The responses were the same in patients not receiving any anti-Parkinsonian therapy as in the remainder, who were receiving only anticholinergics. Reid *et al.* (1971) studying patients aged up to 82 years, not receiving levodopa therapy, confirmed that the Valsalva responses were no different from those expected on the grounds of age. Moreover, there was no correlation between those responses and the duration or severity of the Parkinson's disease.

Introduction of levodopa (Ballantyne, 1973), in younger sufferers from Parkinson's disease caused an early (1 month) reduction in supine blood pressure, which was not sustained at 6 months. There was no increase in the response to tilt, at these times, but the efficiency of the constrictor response to the Valsalva manoeuvre was impaired. Although a parallel group study showed no significant difference in the incidence of postural hypotension between those receiving levodopa alone and those receiving a combination with carbidopa (Leibowitz & Lieberman, 1975), an historical comparison (Barbeau *et al.*, 1971) suggested that the addition of a decarboxylase inhibitor was beneficial in this respect.

Sachs *et al.* (1985) and Goetz *et al.* (1986) studied the time course of response to single doses of levodopa/decarboxylase inhibitor com-

binations in patients undergoing maintenance therapy. There was no treatment effect with respect to supine blood pressure, orthostatic fall or the Valsalva manoeuvre. This was despite overt 'on/off' fluctuations in relation to dopaminergic therapy in Goetz *et al.*'s (1986) patients and definite responsiveness to individual doses in those of Sachs *et al.* (1985). (Although the orthostatic and Valsalva responses were different from those of controls in the former study, they were similar in the latter). In an older patient group, with no overt fluctuation in performance in relation to individual maintenance doses, we were able to confirm their findings with respect to supine pressure and orthostatic response.

Interestingly, in the study of Sachs *et al.* (1985) there was a treatment effect with respect to the increase in diastolic blood pressure produced by isometric hand grip: this was less than in the control subjects and was attenuated by the test

done. They suggest that this might be the result of decreased co-activation of other muscles following medication. In our study, we do not exclude the possibility of an unobserved effect of the nature of treatment on blood pressure during walking.

There are several different patterns of gait in Parkinsonism, irrespective of whether therapy has been commenced (Klenerman *et al.*, 1988; Leeman *et al.*, 1989). The method of gait analysis described allows the gait of an individual to be characterised simply. The study suggests that it might be feasible to identify the predominant reason for a given pattern and to tailor the therapy accordingly.

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