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Parkinson's disease in the elderly: Response to and optimal spacing of night time dosing with levodopa

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1 Insomnia is an even more frequent complaint in elderly patients with Parkinson's disease than might be expected from the effect of age alone on sleep.

2 A double-blind, placebo-controlled trial in eleven patients with Parkinson's disease of mean (s.d.) age 80(5) years, showed that nocturnal dosing with levodopa produced a clinically significant improvement in sleep both as assessed subjectively and by measurement of number of spontaneous moves in bed.

3 Despite the long interval between tablet administration and morning assessment, walking time was faster on mornings following active treatment.

Keywords Parkinson's disease elderly sleep morning performance levodopa

Introduction

Night time is fraught with problems for elderly patients with Parkinson's disease. Difficulty turning in bed is a particularly distressing symptom thereof (Lesser *et al.*, 1979; Stephen & Williamson, 1984) and may lead to functional incontinence and pressure sores. In patients receiving treatment with levodopa, poverty of movement may be exacerbated as a result of an end of dose effect (Marsden & Parkes, 1976) or alleviated by reaccumulation of central dopamine stores during rest (Parkes, 1983). Similarly early morning performance on arising from bed may be influenced adversely or favourably by treatment. Insomnia is a more frequent complaint in Parkinson's disease than might be expected from the effect of age alone on sleep (Kales *et al.*, 1971; Askensay & Yahr, 1983). The association between insomnia and Parkinson's disease has been attributed on the one hand to an unwanted effect of long term levodopa treatment (Sweet & Fletcher, 1975; Lesser *et al.*, 1979; Nausieda *et al.*, 1982) and on the other to inadequate dopaminergic therapy (Askensay & Yahr, 1985). We have carried out a double-blind, placebo controlled, cross-over study of the effects of nocturnal dosing with a levodopa/carbidopa combination on quality of sleep, movement in bed and morning performance in elderly patients with idiopathic Parkinson's disease.

Methods

Patients

Parkinsonism was diagnosed by the presence of two or more of the following signs: tremor, rigidity, bradykinesia and postural abnormality (either flexed posture or impaired postural reflexes). A history of improvement after dopamine replacement therapy was regarded as essential to the diagnosis of idiopathic Parkinson's disease.

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Alternative causes of Parkinsonism were excluded using a flow chart similar to that of Quinn & Husain (1986). Patients in whom there were reservations about the diagnosis were excluded. Informed consent was sought from those eligible for the study.

Design of study

Before entering the study patients were stabilised on the regime of Sinemet-Plus (Merck Sharp and Dohme Ltd, 100 mg levodopa and 25 mg carbidopa per tablet) which appeared to give optimal control of their Parkinson's disease during the day. All patients received a night-time dose of two tablets of Sinemet-Plus at 22.00 h. They were receiving no other anti-Parkinsonian agents. During the study each patient was given the three night-time treatments shown in Table 1 in randomised order. Treatments were for 4 nights with an interval of at least 3 nights between, the initial regimen of two Sinemet-Plus tablets at night being resumed between treatments. Day-time medication remained constant throughout the study.

Assessments

Quality of sleep This was assessed using a visual analogue scale consisting of a line from 'the worst night's sleep I have ever had' on the extreme left, at zero, to the 'best night's sleep I have ever had' on the right at 150 mm. The patients were instructed to mark the middle of the line if they considered their sleep had been normal on the previous night. If the night had been poor, the mark should be made towards the left end of the line and, had it been good, towards the right end, at a distance representative of the grading. In addition the assessor asked whether the patient had been disturbed by pain during the night.

Table 1 Night-time treatments

	Time	
Treatment	*22.00 h*	*0.300 h**
A	2 placebo	1 placebo
B	2 Sinemet-Plus	1 placebo
C	1 Sinemet-Plus 1 placebo	1 Sinemet-Plus

* Designed to assess whether dividing the nocturnal dose between two administration times improved sleep and morning performance by overcoming an end of dose effect.

Measurement of movement in bed

A system involving a load transducer under each bed leg was used to obtain a continuous plot of the lateral position of the patient's centre of gravity (Nicholson *et al.*, 1986). Each transducer consisted of a cantilever, whose deflection was sensed by a resistive strain gauge. The four strain gauge resistor elements were connected in a bridge configuration so that the out-of-balance signal was related linearly to the position of the patient's centre of gravity across the bed (Figure 1). The signal was amplified, filtered and displayed on a chart recorder, giving a continuous plot of the position of the patient's centre of gravity.

The records for the hour after retiring to bed and the hour before arising in the morning were eliminated from the analysis. Rising from and returning to bed during the night produced characteristic deflections: 10 min periods before and after such events were also discarded. A section of trace of the same length was discarded around the times when the subject received attention during the night, such times being noted by the attendant.

The absolute displacement of the patient's centre of gravity was calculated from body weight and a calibration by known weight. A displacement as small as 4 mm could reliably be detected. Only displacements of the patient's centre of gravity greater than this, and sustained for 1 min or longer, were used in the analysis. Drifts of the pen, defined as movements not completed within half a minute or less, were not analysed. For each night studied the number of moves by the patient greater than 4, 10 and 20 mm were counted and all distances of more than 4 mm were summed. The values were adjusted proportionately according to the length of record analysed. The mean size of the movements was also calculated.

Morning assessment The following were measured after each night of the treatment period, before the first day-time (10.00 h) dose of Sinemet-Plus had been given:

(a) Time to walk an (individually) fixed distance. This included the time taken by the patient to transfer from the chair, walk the set distance, return to, and transfer back into the chair. The distance was constant for, and within the known capabilities of, a given subject.

(b) Time for 10 blinks. Three estimations, at least a minute apart, were made whilst the patient was engaged in quiet conversation.

Statistical methods

Analysis of variance was carried out to determine

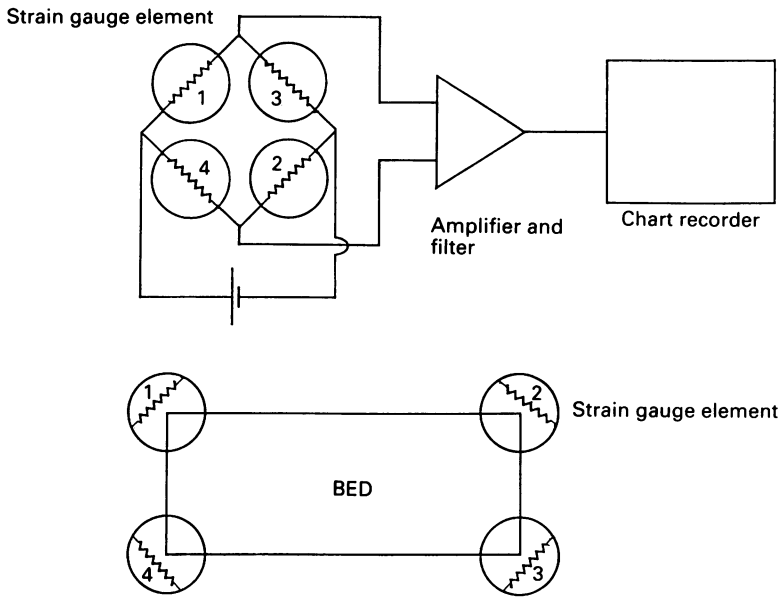

Figure 1 Circuit diagram of bridge arrangement of strain gauge load cells.

the effects of treatment (placebo *vs* the mean of the two Sinemet-Plus regimes, and the difference between the Sinemet-Plus regimes), sequence of administration of the three treatments and any interactions between treatment and sequence. The analysis took into account any incompleteness of data on any treatment. The association between visual analogue measurements of sleep and measures of movement and of morning performance was estimated by calculating the partial correlation coefficient after allowing for differences between patients, treatments and sequence of treatments. Because a large number of significance tests were carried out, only $P < 0.01$ was accepted as statistically significant in this study.

Results

The within patient variances in number of moves in each size category, total distance moved, mean move size, time to walk a set distance and the time for 10 blinks were dependent on the respective mean value in that patient. Analysis of the data following log transformation yielded residuals of constant variance.

Table 2 gives the characteristics of the eleven eligible patients studied and their ratings of quality of sleep on the three treatments. Seven of the eleven judged their sleep to be better on both treatments containing Sinemet-Plus (treatment B and C) than on the placebo treatment (A). The mean ratings on the visual analogue scale for treatments B and C, 93 and 84 mm respectively, indicated a better than average night, whilst the mean rating on A, 67 mm, indicated a worse than average night. There was a highly significant ($P < 0.01$) improvement in quality of sleep on treatments B and C as compared with treatment A, but a marginal improvement on treatment B as compared with C ($P = 0.06$). The improvement was not a consequence of reduced discomfort during the night (Table 2).

There was no significant difference in the number of times the patients rose from bed or were attended to on treatments B and C as compared with A ($P > 0.1$), or on treatment B as compared with C ($P > 0.5$). However, excluding these events, patients made fewer spontaneous moves in bed on treatments B and C, than on A (Table 3). The reduction reached statistical significance at the 1% level for the total number of moves measured but not for the number greater than 10 mm or 20 mm ($P < 0.1$ and $P > 0.1$ respectively). The total distance moved was less on B and C than on A ($P < 0.01$). Mean move size was unaffected by treatment. There was no significant difference between treatments B and C with respect to spontaneous movement during the whole night, or the parts of the night before and after the 03.00 h tablet administration time.

The individually set distance from chair to turning point and back varied from 4 to 12 m

Table 2 Characteristics of patients studied and their assessment of sleep on three treatments: the values given for the visual analogue rating of sleep are the means for the four nights on each treatment

Patient	*Age (years)*	*Hoehn & Yahr staging*	*Duration of levodopa therapy (months)*	*Cognitive function score*	*Quality of sleep on a visual analogue scale (mm)*		
					Treatment A	*Treatment B*	*Treatment C*
1	76	4	32	14	85	120^{+}	92
2	79	4	94	16	48^{+}	90†§	84^{+}†
3	79	3	10	10	126	*	78
4	69	5	17	—	102	*	71
5	78	3	11	14	16	136	146
6	81	5	72	11	54	63	79
7	87	4	6	14	68	85†	64
8	82	4	183	14	69	53	46
9	81	3	5	14	58	135	123
10	81	4	60	8	68	81‡	77
11	83	4	16	13	41	75	67
Mean (s.d.) (11 patients)	80(5)	4(1)	46(54)	13(2)	67(30)	93(30)	84(28)
Mean (s.d.) (excluding two patients*)					56(20)	93(30)	86(31)

— no data.
* final treatment not completed because of intercurrent illness.
Discomfort suffered during night: $^{+}$ leg cramp; † 'burning' pain in heels and/or legs; § parasthesia in legs; ‡ pain like 'a current running through legs'.

mean 8, s.d. 3 metres. Patients walked faster ($P < 0.01$) on the mornings following nocturnal dosing with Sinemet-Plus than on those following placebo (Figure 2). Dividing the nocturnal dose of Sinemet-Plus between the two administration times had no effect on walking time. There was a suggestion that blink time was significantly shorter on active treatment than on placebo. However, significant ($P < 0.01$) interactions between sequence and nature of treatment were present, the implication being that the treatment effect on blink time was dependent on the order of administration. No significant (at the 1% level) effect of sequence of treatment or interaction was seen with respect to the other assessments.

There were significant ($P < 0.001$) negative partial correlations between the visual analogue rating of sleep and the number of moves in the size categories greater than 4 mm, 10 mm and 20 mm and the total distance moved ($r = -0.44$, -0.39, -0.38, -0.40 respectively). Neither mean move size ($r = -0.14$, $P = 0.16$) nor morning performance as judged by walking time and the time for 10 blinks ($r = -0.01$, $P = 1.0$ and $r = 0.04$, $P = 0.5$ respectively) were related to quality of sleep.

Discussion

The validity of clinical trials of anti-Parkinsonian drugs rests heavily on the diagnostic criteria adopted. Once Parkinsonism has been recognised, the clinical diagnosis of idiopathic Parkinson's disease is one of exclusion. Quinn & Husain (1986) make the achievement of at least 50 per cent reversal of the neurological deficit by levodopa (the mode of assessment being unspecified) the final step in their 'clinical algorithm'. However, in geriatric practice the benefits acruing in long-term levodopa therapy and in a late stage of the disease process are often small, variable, and documented only by subjective reports. The eleven patients stuided here were recruited on the grounds of a history of clinical improvement (albeit unquantified) after the introduction of levodopa. Despite the long interval between nocturnal dosing and the objective morning assessment, their performance was found to be significantly better on levodopa than on placebo. We therefore suggest that, with respect to geriatric practice, the emphasis in the above diagnostic scheme would have been more aptly placed on controlled objective demonstration of response to therapy than on arbitrary and often unrealistic expectations of benefit (Quinn & Husain, 1986).

Our ability to discriminate between active and placebo treatments using a timed walking test is attributed to standardisation of the environment in which the test was performed, familarity of the patient with both assessor and test procedure prior to entry into the study, and the selection of

Table 3 Frequency and size of movements in bed on three treatments: the values given for individual patients are the means for the four nights on each treatment

	Treatment A					*Treatment B*					*Treatment C*				
	*Number of moves**		*Total distance moved**	*Mean move size*		*Number of moves*			*Total distance moved*	*Mean move size*	*Number of moves*			*Total distance moved*	*Mean move size*
Patient	*> 4 mm*	*> 10 mm*	*> 20 mm*	*(mm)*	*(mm)*	*> 4 mm*	*> 10 mm*	*> 20 mm*	*(mm)*	*(mm)*	*> 4 mm*	*> 10 mm*	*> 20 mm*	*(mm)*	*(mm)*
1	12	5	2	159	14	12	3	1	118	9	11	5	2	137	13
2	39	17	8	694	19	15	8	5	316	22	21	11	6	454	21
3	12	6	3	197	15	—	—	—	—	—	16	8	3	221	14
4	19	7	2	225	12	—	—	—	—	—	42	23	10	701	18
5	68	47	24	1389	20	11	6	2	154	13	18	10	3	170	13
6	16	6	1	146	9	17	8	1	175	10	10	4	1	101	11
7	13	8	0	162	13	7	4	1	85	12	8	5	1	106	10
8	23	11	4	322	14	28	16	10	967	36	33	15	8	576	18
9	23	16	10	520	22	16	10	7	375	21	10	4	2	151	15
10	24	12	4	319	13	23	13	3	289	12	31	20	8	505	16
11	10	6	5	381	39	11	7	6	360	33	7	5	3	218	33
Mean	24	13	6	410	17	16	8	4	315	19	19	10	4	304	17
s.d.	17	12	7	366	8	7	4	3	267	10	12	7	3	214	6

* Adjusted proportionately to give values for a 6 h period.

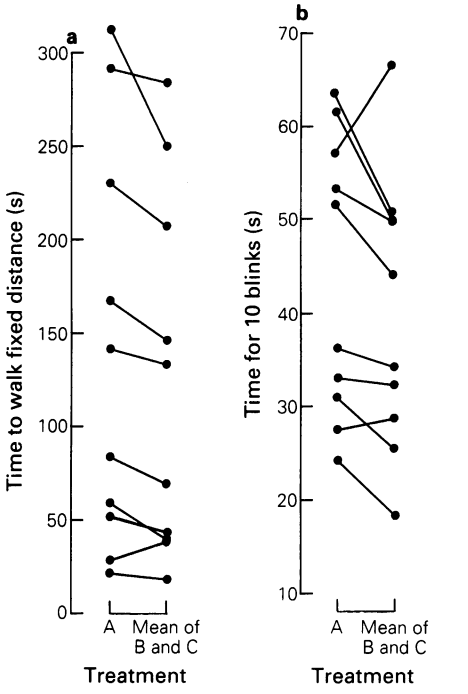

Figure 2 Comparison of (a) time to walk a fixed distance and (b) time taken for 10 blinks following nocturnal dosing with placebo (treatment A) and Sinemet-Plus (treatment B and C). The values given are the means for the four mornings studied on treatment A and the eight on treatments B and C, except in the case of patient 3 where only data for treatments A and C were available. Data from patient 4 were excluded from the figure because of the long time taken in both walking and blink tests. He walked faster on the only active treatment completed, treatment C, (649 s to walk a fixed distance) than on A (797 s) and took less time for 10 blinks on C than on A (197 and 295 s, respectively).

a distance to be walked which was tailored to the capabilities of each subject. Without this attention to detail a timed walking test is even less sensitive to drug effects than a global rating of disease severity (Mindham, 1976). However, the results of the timed walking test did not distinguish between the two spacing options for active treatment. Reduction in blink rate has been reported to correlate well with severity of akinesia in patients with fluctuating akinesia (Delwaide *et al.*, 1984; Karson *et al.*, 1984). The test has the advantage of being quick and requires no co-operation from the patient. However, in our experience, blink rate was too labile to serve as a reliable index of treatment effect.

Nocturnal administration of levodopa resulted in an improvement in the subjective assessment

of sleep. Spontaneous movement decreases during sleep (Cox & Marley, 1959) the magnitude of the effect being dependent on the depth of sleep (Loomis *et al.*, 1937; Blake *et al.*, 1939). Thus the reduction in number of movements in bed by levodopa therapy simply confirms that the duration and/or depth of sleep was greater. Hypnotics such as barbiturates, meprobamate and flurazepam not only reduce spontaneous movement during the night but can also impair mobility on the following day (Hinton & Marley, 1959; Hinton, 1961; Crowley & Hydinger-Macdonald, 1979). The beneficial effect of nocturnal dosing with levodopa on morning performance suggests that its hypnotic-like effect is secondary to improvement in control of Parkinson's disease. Lees *et al.* (1977) found that difficulty in turning voluntarily during the night was responsive to dopaminergic therapy. The patient's improved ability to turn in bed may allow a more comfortable position to be adopted. This together with the knowledge that he could more easily change his position may be conducive to sleep. Lakke *et al.* (1980) did however find that difficulty in axial rotation in the recumbent position persisted into the day despite otherwise adequate replacement therapy. Studies in elderly non-Parkinsonian subjects with similar degrees of sleep disturbance would determine whether or not the hypnotic-like effect which we reported was simply secondary to better control of Parkinson's disease.

Electromyography has shown that striated muscle activity is markedly increased during sleep in Parkinson's disease. Not only is there an increase in repetitive muscle contraction in limbs, but also in burst tremor (clincally accompanied by a jerk) and in periodic nocturnal myoclonus (Askensay & Yahr, 1983). Abnormal sensations of pain, tingling, numbness and burning are themselves common and distressing manifestations of Parkinson's disease (Snider *et al.*, 1976). These phenomena have been ascribed both to too excessive and to inadequate doses of levodopa (Kales *et al.*, 1967; Askensay & Yahr, 1985; Quinn *et al.*, 1986). In our patients discomfort and pain were, in fact, more common accompaniments of active than of placebo treatment: the improved sleep on levodopa could not be explained by a diminution in these symptoms.

Electroencephalographic (EEG) studies show that the elderly take longer to get to sleep than younger subjects, have an increased number of awakenings, take longer to get back to sleep and have a reduced length of sleep. The proportion of deep to light sleep decreases, but that of rapid to non-rapid eye movement sleep is unchanged (Kales *et al.*, 1967; Herbert, 1978). In Parkinson's disease the pattern of light and fragmented sleep is similar, but is more pronounced than expected on the grounds of age (Kales *et al.*, 1971; Askensay & Yahr, 1983). The effect of levodopa on the sleep pattern in Parkinson's disease has been controversial (Askensay & Yahr, 1985). Problems in interpretation of EEG studies arise from the use of ill-defined diagnostic categories, inadequate experimental design, and the failure to present either raw data or adequate statistical analysis.

Bergonzi and coworkers (1974) found that patients receiving high doses of levodopa showed arousal, whereas others taking average dosages slept better than when untreated. Reversal of effect at higher doses might also explain reports of an increased incidence of insomnia, nightmares, restlessness and reflex daytime somnolence in patients on the maximum doses tolerated or longterm levodopa therapy (Jenkins & Groh, 1970; Horvath & Meares, 1974; Nausieda *et al.*, 1982). The altered response at high doses may represent the effect of dopamine on differing dopaminergic receptors, on other classes of receptor or its metabolism to other neurotransmitters. Claims of differing effects of other dopaminergic agents (Askensy & Yahr, 1985) need to be confirmed by clinical trials.

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