Effect of Age and Arteriosclerosis on the Response of Parkinsonian Patients to Levodopa

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British Medical Journal, 1971, 4, 522-524

Summary

Twenty-four patients with Parkinsonism were treated with levodopa for up to one year. Ten were aged under 65, 12 were aged 65 or over, and two were specifically included because they were considered to have arteriosclerotic Parkinsonism. These two patients showed no response to treatment. The 10 younger patients showed less clinical evidence of arteriosclerosis than the older ones, and responded significantly better to treatment with levodopa. Mean improvement was 61% in the younger group after 12 months' treatment and 28% in the older group. Improvement was greatest within three months of starting treatment. Abnormal movements which resulted from treatment with levodopa could be reduced with only slight loss of therapeutic benefit by the addition of tetrabenazine.

Introduction

The suggestion that cerebral arteriosclerosis may be a cause of Parkinsonism was made by Critchley (1929), who defined the clinical criteria for this diagnosis. Previous authors had mentioned arteriosclerosis as a cause of Parkinsonism (Brissaud, 1895; Lewy, 1913; Souques, 1921) and since Critchley's description the definition of arteriosclerotic Parkinsonism has been extended, so that Garland (1955) considered 21% of his cases to be of arteriosclerotic aetiology. Eadie and Sutherland (1964) showed no excess of clinically detectable arterial disease in a group of patients with Parkinsonism and cast doubt on the concept of arteriosclerosis as a cause but agreed that their cases did not conform to the clinical definition made by Critchley (1929). Such cases are much less commonly seen than patients with idiopathic Parkinsonism, and in any investigation designed to study therapeutic effects the associated arteriosclerotic features such as dementia and hemiplegia make clinical assessment of disability attributable to extrapyramidal deficit very difficult and the assessment of response to treatment unreliable.

Levodopa has been shown to be the most effective medical treatment for most patients with idiopathic Parkinson's disease (Calne, Spiers, Stern, Laurence, and Armitage, 1969; Cotzias, Papavasiliou, and Gellene, 1969; Godwin-Austen, Tomlinson, Frears, and Kok, 1969; Yahr, Duvoisin, Schear, Barrett, and Hoehn, 1969) and postencephalitic Parkinsonism (Calne, Stern, Laurence, Sharkey, and Armitage, 1969). The Parkinsonian syndrome resulting from chronic manganese toxicity has also been shown to be alleviated by levodopa (Mena, Court, Fuenzalida, Papavasiliou, and Cotzias, 1970). In a previous investigation (Godwin-Austen, Frears, and Bergmann, 1971) we found that patients with Parkinsonism aged 65 or over tolerated a lower mean dose of levodopa than younger patients. We now wish to report an investigation into the effect of age and arteriosclerosis on the response of patients with Parkinsonism to treatment with levodopa.

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Methods

Twenty-four patients (10 women and 14 men) aged 46 to 79 were admitted to the trial after full discussion with the patients and their relatives. They were selected from the diagnostic index of the National Hospital, Queen Square, so that there were about equal numbers of patients aged under 65 and 65 or over. In addition, two patients were included who had arteriosclerotic Parkinsonism but were without dementia or significant neurological deficit other than their extrapyramidal syndrome. The diagnosis in these two cases was agreed by two neurologists on the basis of sudden onset and stepwise progression of symptoms, features of generalized arteriosclerosis, associated features such as *marche à petits pas* and pseudobulbar manifestations, and the absence of tremor. Both these patients were aged over 65 years.

All patients were initially assessed in the outpatient department. They were excluded from the trial if there was either disability likely to interfere with neurological assessment but not attributable to Parkinsonism or cardiac disease (including arrhythmia) or if they were on treatment with monoamine oxidase inhibitors. The patients were admitted to hospital and started on treatment with levodopa, their other medications remaining unaltered. They were discharged after two weeks' treatment and followed in the outpatient department at fortnightly intervals for three months and at monthly intervals thereafter. At each attendance the patient was questioned about side effects and examined (including lying and standing blood pressure); the urine was tested for albumin and glucose; and blood was taken for blood film, direct Coombs test, and serum alkaline phosphatase and serum aspartate aminotransferase estimation.

The outpatient assessments of disability from Parkinsonism were carried out before starting treatment and further assessments were done after 3, 6, 9, and 12 months of continuous levodopa therapy. The method of assessment of Parkinsonism was the same as that used for an earlier trial (Godwin-Austen *et al.*, 1969), but no attempt was made to conduct these assessments blind. The ages of the patients and the diagnosis in the two cases of arteriosclerotic Parkinsonism were known to the examining physician at the time of assessment of disability from Parkinsonism. An assessment of arteriosclerosis was adopted by using the following clinical criteria: (1) diastolic blood pressure—scored 0 if less than 90 mm Hg, 1 if between 90 and 105 mm Hg, 2 if between 106 and 120 mm Hg, and 3 if greater than 120 mm Hg; (2) retinal arterial disease scored by the grading described by Keith, Wagener, and Barker (1939); (3) absence of peripheral pulses or major arterial bruits (scores 0, 1, or 2); and (4) ischaemic myocardial changes on E.C.G. (scored 0 or 1). It was appreciated that these criteria are an insufficient estimate of arteriosclerosis but they provide a simple assessment such as the clinician customarily uses.

Results

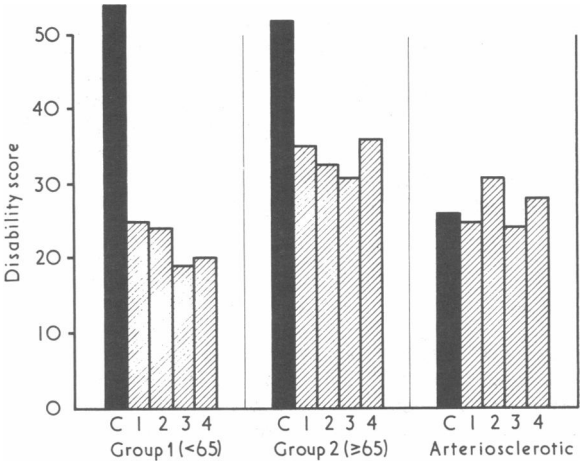
Out of 24 patients admitted to the trial five discontinued treatment within the 12-month period, but all except two completed three months of treatment. These two patients were

unable to co-operate with the frequent outpatient attendances and spontaneously failed to take their prescribed treatment.

The response to treatment of the two patients with arteriosclerotic Parkinsonism was assessed separately. Of the 20 other patients 10 were aged under 65 (group I) and 10 were 65 or over (group II). One patient in each group was withdrawn from the trial after three months' treatment as the result of toxic effects from levodopa which are described below. One patient aged over 65 died during the trial from cerebral haemorrhage. She had responded extremely well to treatment and from being severely disabled and dependent on her husband for all domestic tasks became independent and mobile. During the seventh month of treatment she became confused and levodopa was withdrawn. Three weeks later she became unrousable and died shortly after.

One patient in group I, after a dramatic response to treatment and continuing improvement at six months, fell and fractured his femur. Subsequent assessments of response were therefore unreliable.

Ten patients in each group were therefore available for assessment after three months' treatment and eight patients in each group were available for assessment after 12 months' treatment.



Disability scores in the three groups of patients at the control assessment before treatment (C) and at the four subsequent assessments after 3, 6, 9, and 12 months of treatment with levodopa.

DOSE

The maximum tolerated dose ranged between 0·65 and 6 g daily. At the three-month assessment the mean daily dose in group I was 4·0 g and in group II 2·6 g. After 12 months' treatment the mean for group I was 3·6 g daily and for group II 2·1 g daily. Thus the younger patients were able to tolerate a higher mean dose of levodopa than the more elderly patients (see also Godwin-Austen *et al.*, 1971) and there was a tendency for the tolerated dose to become less during the course of the trial. There was no correlation between tolerated dose of levodopa and clinical response but patients unable to tolerate more than 1 g daily did not show more than minimal improvement.

ARTERIOSCLEROSIS

When the patients were assessed for clinical evidence of arteriosclerosis the scores ranged from 0 to 5. Only two patients in group I showed any of the features listed as criteria for arteriosclerosis. One of these had retinal changes and absent peripheral pulses in the legs and had to be withdrawn from the trial after three months because of cardiac arrhythmia. In group II (patients aged 65 or over) all but one showed clinical evidence of arteriosclerosis. There was therefore a very clear difference between the two groups on the basis of clinical evidence of arterial disease. The patient who showed most evidence of arteriosclerosis was one of the two patients suffering from arteriosclerotic Parkinsonism.

THERAPEUTIC EFFECTS

The mean disability score before treatment in group I was 55·7 ± 14·8 and in group II 56·3 ± 23·1 so that the pre-existing severity of Parkinsonism in the two groups was comparable. Most patients responded well to treatment and in some cases improvement was considerable. Thus seven patients improved by more than 50% of their initial disability score and only five showed improvement of less than 20% of their pretreatment score. These five patients who responded poorly to treatment were all aged 65 or over and two of them were the patients with arteriosclerotic Parkinsonism.

The responses of the three groups of patients to treatment are illustrated in the Chart. The response to treatment of group I was better than that of group II and this difference in response at 12 months is significant ($P < 0.01$). The mean improvement in group I was 61% and in group II 28%. In both groups the greatest benefit occurred within the first three months and no further significant improvement occurred subsequently. In group II, however, there was a tendency for benefit from treatment to be slightly less towards the end of the 12-month trial period, though this deterioration did not reach levels of significance. There were no patients who failed to improve after three months' treatment but who subsequently responded. Patients who showed no clinical evidence of generalized arteriosclerosis showed an improvement in mean disability score at three months of 31·2 compared with a mean improvement of 19·8 for the arteriosclerotic patients. This difference is not significant ($P < 0.1$). However, at the 12-month assessment the differences were significant (34·1 and 12·8 respectively, $P < 0.01$), indicating a more favourable response among the non-arteriosclerotic patients. There was no direct correlation between severity of arteriosclerosis and response to treatment.

The results of treatment for 12 months were analysed further into four subgroups (see Table). Functional disability was measured by the patient's assessment of his own independence at home for tasks such as dressing, feeding, hygiene, walking, and writing. In group I there was significant improvement ($P < 0.05$) but in group II the mean improvement did not reach levels of significance and three patients showed no improvement in functional disability. There was significant benefit in group I when these patients were assessed for tremor, rigidity, and bradykinesia but in group II the mean improvement was much less, and only improvement in tremor reached levels of significance ($P < 0.05$). Tremor was significantly improved in group I within three months of starting treatment and little further improvement in tremor was recorded up to six months of continuous treatment. No relapse in subsection scores was noticed in either group during the period of observation. Those patients who derived benefit from levodopa seemed to do so in all respects, whereas those who did not respond or in whom the response in aggregate was only slight showed little or no benefit in subsection scores.

Mean Improvement

	Group 1, aged <65	Group 2, aged ≥65
Functional disability	66%	27%*
Bradykinesia	56%	35%*
Rigidity	60%	25%*
Tremor	89%	47%

*Not significant. $P > 0.05$.

The three patients in group II who showed only slight improvement were not distinguishable on clinical grounds from the other patients in this series. Their mean pretreatment disability score

was slightly less than the mean score for group II and measure of blood pressure and clinical evidence of arteriosclerosis did not distinguish them from the other patients in group II. However, the two patients considered to be suffering from arteriosclerotic Parkinsonism showed no evidence of benefit from levodopa at any stage of the trial, nor did the assessment of any of the subgroup scores in these cases show improvement. One of these patients deteriorated while on treatment.

TOXIC EFFECTS

The side effects from levodopa which limited dose were nausea and vomiting, abnormal movements, postural hypotension, and confusion and hallucinations as reported previously (Godwin-Austen *et al.*, 1971). The maximum tolerated dose in each patient was established within three months of starting treatment, and in most patients only minimal adjustments of dose were subsequently necessary. The mean dose at three months was 2·8 g daily and at 12 months 3·1 g daily. During the trial two patients required a reduction in dose by more than 1 g daily. One patient aged 47, as the result of severe abnormal movements, required a reduction in dose of levodopa from 4 to 2·5 g daily, and could tolerate this dose only when given tetrabenazine. This drug was given in combination wih levodopa to four patients in an attempt to reduce abnormal movements without reducing the dose of levodopa. One patient developed depressive symptoms attributable to the tetrabenazine so it was withdrawn. In the other patients abnormal movements from levodopa were either greatly improved or, in two cases, abolished by concurrent administration of tetrabenazine in a dose of between 50 and 100 mg daily.

Treatment with this drug in combination with levodopa was continued in these cases for the duration of the trial without loss of effect and has been continued for between 7 and 11 months in all with continuing benefit. The addition of tetrabenazine to the patient's treatment was known to the physician assessing the response of the patient to treatment. There was a slight reduction in the benefit from levodopa when tetrabenazine was added but this was less than the loss of benefit which followed any reduction in the dose of levodopa.

Two patients had to be withdrawn from the trial shortly after the three-month assessment, one as a result of a toxic confusional state and another after the development of cardiac arrhythmia. Three patients developed depression as a late side effect but responded to the addition of tricyclic antidepressants; in three other patients small reductions in dose were necessary because of nausea uncontrollable with antiemetics—promethazine theoclate (Avomine) or metoclopramide (Maxolon).

Discussion

There has been a tendency for some of the early optimism concerning the treatment of Parkinsonism with levodopa to wane. This may be because not all patients show a significant therapeutic response to treatment and because the emergence of late side effects, particularly abnormal movements, may compel a reduction in dose to levels where little or no therapeutic effect is noticeable. The selection of patients suitable for treatment might avoid some of the disappointing results, and age of the patient and arteriosclerosis seem to be important factors.

The results reported here indicated that those aged 65 or over show less therapeutic response to levodopa than younger patients, and this response is independent of tolerated dose or severity of their Parkinsonism. Two patients with arteriosclerotic Parkinsonism failed to show any response to treatment with levodopa. Cotzias *et al.* (1969) were unable to find any correlation between age or arteriosclerosis and response to levodopa but subsequent workers have shown that degree of improvement is inversely related to both age (Peaston and Bianchine, 1970) and hypertension (Hughes, Polgar, Weightman, and Walton, 1971). Our results suggest that elderly or arteriosclerotic patients suffering from a Parkinsonian syndrome respond less well to levodopa than patients who show uncomplicated features of idiopathic Parkinsonism. Age alone, however, does not preclude a satisfactory response to treatment and our group of patients aged 65 or over improved by an average of 28%.

Response to treatment in both groups has occurred within three months of starting treatment and there was no significant further improvement in total score over the subsequent nine months. Two patients aged less than 65, however, continued to show increasing benefit up to 12 months of continuous treatment. This finding confirms the observations of Yahr, Duvoisin, Hoehn, Schear, and Barrett (1968) and Peaston and Bianchine (1970). No patient who ultimately benefited from treatment with levodopa has failed to show improvement before the three-month evaluation. And those patients who derived no benefit from treatment with levodopa for 12 months (including the two patients with arteriosclerotic Parkinsonism) showed no significant improvement at the previous assessments.

Though some patients required a small reduction in dose over the period of treatment there was no significant reduction in dose in either group. Abnormal movements were an important reason for reducing dosage, but we were impressed by the value of the concurrent administration of tetrabenazine. This combined treatment led to slight reduction in the therapeutic effect of levodopa but allowed higher dosage to be maintained with partial amelioration of abnormal movements. Barbeau (1970) suggested that abnormal movements result from the action of dopamine on catecholamine receptors both in the striatum and extrastriatally. Tetrabenazine is known to deplete cerebral dopamine (Pletscher, Brossi, and Grey, 1962) and may thus reduce abnormal movements from levodopa therapy by dopamine depletion extrastriatally.

The other major side effects of prolonged levodopa treatment are nausea and depression and both can in most cases be controlled by the use of antiemetics and tricyclic antidepressants respectively.

We wish to acknowledge with thanks the help of Mrs. C. Howland with the statistical analysis and of Sister M. Ross in the organization of the trial. We are grateful to Roche Products Ltd. for supplies of levodopa (Larodopa).

The investigation was conducted under the auspices of the Medical Research Council's Working Party on Levodopa.

References

Barbeau, A. (1970). *Neurology (Minneapolis)*, **20**, 377.
Brissaud, E. (1895). *Leçons sur les Maladies Nerveuses*. Paris, Masson.
Calne, D. B., Spiers, A. S. D., Stern, G. M., Laurence, D. R., and Armitage, P. (1969). *Lancet*, **2**, 973.
Calne, D. B., Stern, G. M., Laurence, D. R., Sharkey, J., and Armitage, P. (1969). *Lancet*, **1**, 744.
Cotzias, G. C., Papavasiliou, P. S., and Gellene, R. (1969). *New England Journal of Medicine*, **280**, 337.
Critchley, M. (1929). *Brain*, **52**, 23.
Eadie, M. J., and Sutherland, J. M. (1964). *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 237.
Garland, H. (1955). *Proceedings of the Royal Society of Medicine*, **48**, 867.
Godwin-Austen, R. B., Frears, C. C., and Bergmann, S. (1971). *British Medical Journal*, **1**, 267.
Godwin-Austen, R. B., Tomlinson, E. B., Frears, C. C., and Kok, H. W. L. (1969). *Lancet*, **2**, 165.
Hughes, R. C., Polgar, J. G., Weightman, D., and Walton, J. N. (1971). *British Medical Journal*, **1**, 7.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *American Journal of the Medical Sciences*, **197**, 332.
Lewy, F. H. (1913). *Deutsche Zeitschrift für Nervenheilkunde*, **50**, 50.
Mena, I., Court, J., Fuenzalida, S., Papavasiliou, P. S., and Cotzias, G. C. (1970). *New England Journal of Medicine*, **282**, 5.
Peaston, M. J. T., and Bianchine, J. R. (1970). *British Medical Journal*, **1**, 400.
Pletscher, A., Brossi, A., and Grey, K. F. (1962). *International Review of Neurology*, **4**, 275.
Souques, A. (1921). *Revue Neurologique*, **28**, 534.
Yahr, M. D., Duvoisin, R. C., Hoehn, M. M., Schear, M. J., and Barrett, R. E. (1968). *Transactions of the American Neurological Association*, **93**, 56.
Yahr, M. D., Duvoisin, R. C., Schear, M. J., Barrett, R. E., and Hoehn, M. M. (1969). *Archives of Neurology*, **21**, 343.