Audit of the drug treatment of Parkinson's disease in general practice

JOHN A. WILSON, MB
Trainee General Practitioner, Glasgow Western Vocational Training Scheme

T.S. MURRAY, FRCP, FRCGP
Associate Adviser in General Practice, Glasgow Western District

SUMMARY. In a general practice population of 57 000, 32 patients suffering from Parkinson's disease were identified from repeat prescription indexes and direct questioning of all members of the primary health care team. Of these patients 26 were receiving an L-dopa preparation and 10 an anticholinergic drug. The only newer drug found to be in use was bromocriptine and three patients were receiving this treatment.

Of the 26 patients receiving an L-dopa preparation one received L-dopa alone, six L-dopa with benserazide (Madopar, Roche) and 19 L-dopa with carbidopa (Sinemet, Merck, Sharp and Dohme). The patients treated with Sinemet were receiving inadequate doses of carbidopa — three quarters received less than 75 mg per day which was in part a reflection of the low doses of L-dopa the patients received, the average dose being 468 mg per day. The L-dopa preparations were given in adequately spaced doses.

The general practitioner made the diagnosis in 20 of the 32 cases and was in control of the drug therapy in 15 cases, however 25 cases were referred for specialist advice.

Introduction

SINCE the discovery of striatal dopamine loss in parkinsonian brains by Ehringer and Hornykiewicz in 1960[1] Parkinson's disease has been the subject of extensive research as it represents the only true degenerative disease of the nervous system for which any form of rational replacement therapy exists.

However the intial hopes that L-dihydroxyphenylalanine (L-dopa) combined with a dopa-decarboxylase inhibitor might represent a cure for Parkinson's disease have disappeared with the re-emergence of various forms of akinesias most notably the 'on-off' phenomenon which may occur after more than three years of L-dopa treatment. Such side effects necessitate increasing the doses of L-dopa causing dyskinesias and increased dementia for elderly patients who may already be confused. It now seems likely that early treatment with L-dopa hastens the appearance of these side effects.[2,3]

More recently it has been shown that at least 75 mg of dopa-decarboxylase inhibitor (carbidopa or benserazide) should be given to completely block the peripheral decarboxylation of L-dopa thus ensuring maximum effectiveness of L-dopa with a minimum of adverse peripheral effects.[3-5] The original formulation of Sinemet (Merck, Sharp and Dohme; L-dopa with carbidopa) contained 10 parts L-dopa to one part carbidopa and this necessitated a minimum daily L-dopa dosage of 750 mg to provide the recommended 75 mg of carbidopa. This is too large a dose of L-dopa for many patients, particularly the elderly, and in many cases it is more appropriate to prescribe a preparation containing four parts L-dopa to one part dopa-decarboxylase inhibitor as in Madopar (Roche; L-dopa with benserazide) or Sinemet-Plus (Merck, Sharp and Dohme).

Bromocriptine has also been the subject of much recent research which has shown a fairly high incidence of side effects, the most troublesome being nausea, confusion (including psychotic states) and postural hypotension.[6] However, as studies on advanced L-dopa treated parkinsonian brains have demonstrated a greater loss of presynaptic neurones (through which L-dopa must act) than post-synaptic receptor sites (which can be directly stimulated by bromocriptine)[7] the place of bromocriptine therapy at present would seem to be in advanced L-dopa treated Parkinson's disease when L-dopa is causing side effects. Research work demonstrates that bromocriptine allows a reduction in L-dopa dosage and hence side effects while producing an overall beneficial therapeutic response.[8]

Recent research has also demonstrated the use of L-deprenyl (a selective monoamine-oxidase type B inhibitor) which inhibits the breakdown of dopamine thus potentiating the effects of relatively low doses of L-dopa, allowing it to produce a smoother therapeutic response.[9]

In parkinsonian brains, in addition to the relative deficiency of the dopaminergic system, there is thought to be a relative overactivity of the cholinergic system hence the extensive use of anticholinergic drugs since the 1940s. Although these drugs are much less effective than L-dopa they are suitable for early treatment where the symptoms are mild. However, in long-standing cases their beneficial effect is lost and they frequently cause confusion which is the major contra-indication to their use; other contra-indications are prostatism and glaucoma.

The antiviral drug amantidine is thought to act by increasing dopamine release hence providing its beneficial therapeutic effect in parkinsonism. Amantidine may cause confusion especially in the elderly but the main limiting factor in the use of this drug is the diminution of its effect which is thought to start after only eight weeks of treatment.[10]

With such a wealth of recent research and therapeutic regimes available it was decided to investigate how patients with Parkinson's disease were managed in general practice in an urban area.

Method

The study was based in the Clydebank Health Centre which houses the surgeries of all 26 general practitioners who look after the Clydebank population of approximately 57 000 patients.

Identification of the patients suffering from Parkinson's disease was a problem. Most practices have an efficient repeat prescribing system and most patients were identified by carefully checking through each repeat prescription to see if it contained any drug which might be used in the treatment of Parkinson's disease. However, four practices (six general practitioners) did not have a repeat prescription index and so a note of all the relevant drugs were left with the receptionists who complete the prescriptions. In addition the general practitioners, district nurses, geriatric nurses and all those running old peoples homes in the area were asked if they could suggest any other patients who might suffer from Parkinson's disease.

Having identified the patients their case notes were examined in order to determine the diagnostic criteria for Parkinson's disease.

Results

Of the total population of approximately 57 000 32 patients were identified as suffering from Parkinson's disease. The details of their drug treatment are given in Table 1. Twenty-nine patients were receiving anti-parkinsonian medication and of these 26 were receiving treatment with an L-dopa preparation — one was being treated with L-dopa alone, six were being treated with Madopar while 19 were being treated with Sinemet. However, only three of the latter 19 patients were receiving Sinemet-Plus. Table 2 shows the amount of carbidopa received by the patients treated with Sinemet. Only four of the 19 patients treated with Sinemet were receiving enough carbidopa to completely block the peripheral decarboxylation of L-dopa.

Table 1. Drug treatment of the 32 patients suffering from Parkinson's disease.

Drug group	Number of patients	Average age of patients (years)
L-Dopa preparations	26	70.5
Anticholinergics	10	65.7
Bromocriptine	3	71.0
Amantadine	3	63.0
Antidepressants	4	75.5
Minor tranquillizers	7	68.8
Major tranquillizers	2	74.3
Antihistamines	1	60.0
No treatment	3	74.3

Average age of all patients is 70.9 years.

Table 2. The amount of carbidopa received by the 19 patients treated with Sinemet.

Dose of carbidopa (mg)	Number of patients
Inadequate	
0–24	3
25–49	6
50–54	5
Uncertain	
75–99	1
Adequate	
100–124	3
125–149	0
⩾150	1

The average dose of L-dopa the patients were receiving was 468 mg per day. However, a few patients were receiving very large doses thus making a considerable difference to the average dose — nearly half of the patients were receiving less than 400 mg per day. Figure 1 shows the number of times L-dopa was given in a day and it can be seen that most of the patients were receiving their L-dopa dosage at widely spread intervals.

The diagnosis of Parkinson's disease was made by the general practitioner in most instances and the general practitioner was found to be the person most frequently responsible for controlling the medication of the patient (Table 3). However, the general practitioners had received help with the treatment of most of the patients. Of the 32 patients 25 had been referred for specialist advice and some had been referred to more than one department. The 25 patients who had been referred amassed a total of 31 referrals (Institute of neurological sciences, 14; medical outpatients department, 8; geriatric service, 7; psychiatry, 2). Only seven patients had not seen a specialist and all of these patients had at least two major and one minor or one major and two minor manifestations of Parkinson's disease.[5]

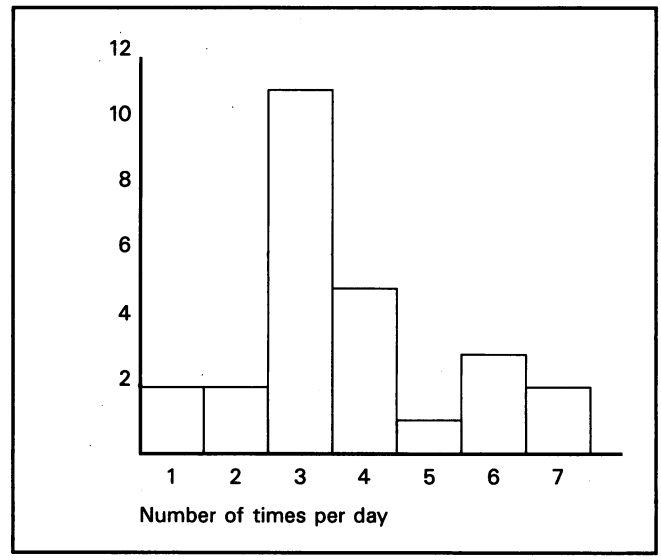

Figure 1. *Number of times L-dopa was given in a day*

The overall prevalence of Parkinson's disease was found to be 0.65 per 1000 practice population. Exclusion of the practices where no patients suffering from Parkinson's disease were discovered (those practices without a repeat prescription index), resulted in a total population of 40 169 giving a prevalence of 0.80 per 1000. The 32 patients came from five practices (20 general practitioners) — the prevalence in each of these being 0.72 per 1000; 0.65 per 1000; 1.22 per 1000; 0.59 per 1000 and 0.62 per 1000.

Table 3. Where the initial diagnosis was made and where drug therapy controlled.

	Initial diagnosis	Control of drug therapy
	Number of patients	Number of patients
General practice	20	15
Medical outpatients department	5	4
Institute of neurological sciences	4	9
Geriatric services	3	4

Discussion

As expected, the study confirmed that combined L-dopa preparations are the primary treatment for Parkinson's disease. More patients were being treated with Sinemet than Madopar despite recent studies which reported that it is difficult to distinguish between the two in terms of efficacy.[11,12]

It is interesting to note that 10 patients (one-third of the treated patients) were receiving an anticholinergic drug despite the extensive side effects reported in the literature for this group of drugs especially when used to treat the elderly. The average age

of the patients in the study was 70.9 years, and the average age of those receiving anticholingergics (65.7 years) was lower than those who were not (72.7 years). It would seem from this study that anticholinergic drugs form the second line of treatment.

The use of the newer drugs was rather disappointing. Only three patients (10 per cent of the treated patients) were receiving bromocriptine. Although bromocriptine is free from some of the long-term side effects of L-dopa the appearance of earlier side effects may discourage its use. The percentage of patients being treated with bromocriptine was greater than the percentage found in a similar larger scale study based in geriatric units and carried out by White and Barnes who found that only five per cent of treated patients were receiving bromocriptine.[13] However, White and Barnes found a similar percentage of patients — 33 per cent — were being treated with anticholinergics.

It is rather surprising that three patients (10 per cent of the treated patients) were receiving amantadine as its beneficial effects are so transient. The main use of amantadine is to delay the introduction of L-dopa treatment yet of the three amantadine treated patients, two were also receiving treatment with L-dopa.

The four patients receiving concurrent antidepressive treatment reflects the association of Parkinson's disease with depressive illness. Fortunately, only two patients were receiving major tranquillizers, which act as dopamine blocking agents thus exacerbating Parkinson's disease (in both cases the tranquillizers were introduced after treatment with L-dopa had commenced).

One patient was receiving treatment with an antihistamine preparation, promethazine hydrochloride (Phenergan 25 mg b.d.), which has a similar effect to the anticholinergic drugs. However, it is slightly less effective but slightly better tolerated than the anticholinergics especially by elderly patients who may benefit from the sedative effect.[10]

As shown in Table 2 only four of the patients treated with Sinemet were receiving enough carbidopa to completely block the peripheral decarboxylation of L-dopa; this is partly due to the preference for giving low doses of L-dopa. Yet, even with Sinemet-Plus, to receive an effective dose of carbidopa the patient must take at least 300 mg of L-dopa. Nearly half of our patients received less than 400 mg of L-dopa per day (according to Franz the recommended dose of L-dopa to provide an effective dose of carbidopa is 400 to 1200 mg per day[14]). Certain parkinsonian patients, especially the elderly, may respond to tiny doses of L-dopa and may become confused when this is increased.

As Parkinson's disease progresses fluctuations in motor performance become more marked and unpredictable and the period of relief from each dose of drug becomes progressively shorter. The main limiting factor in increasing the total daily dosage is the appearance of abnormal involuntary movements shortly after the drug is given, hence current opinion favours the administration of smaller doses of L-dopa three to six times per day. Figure 1 shows that most of the patients were receiving their treatment in adequately spaced doses. This is in marked contrast to the results of White and Barnes[13] who found that more than half their patients received their L-dopa preparations once or twice per day. Of the four patients receiving inadequately spaced doses two received therapy from physicians, one from a general practitioner and one from a geriatrician. All the patients receiving therapy from neurologists were receiving adequately spaced doses of L-dopa preparations.

In most cases the initial diagnosis was made by the general practitioner who was also most frequently in control of the patients' drug therapy (Table 3). However only seven patients were referred to a specialist and several of these were early cases and therefore may not have been at a stage to require referral.

The prevalence of Parkinson's disease is difficult to assess but the national average is probably about 1.0 per 1000 population.[15] In this study it was found to be 0.65 per 1000 practice population. Even when the practices with no record of patients suffering from Parkinson's disease were excluded the prevalence was still only 0.8 per 1000. The practices with patients suffering from the condition had prevalences varying from 0.59 per 1000 to 0.72 per 1000 with the exception of one practice which had a prevalence of 1.22 per 1000. The latter is the only practice with a prevalence above the national average — this may be due to a more elderly practice population. Parkinson's disease is notoriously difficult to diagnose, especially in the elderly. As the variation between the practices is so marked and all the practices are in the same area there may well be underdiagnosing of the condition in some practice populations.

Few of the most recent advances are used in general practice. However, it would seem from the findings of this small study that although the diagnosis of Parkinson's disease can pose major problems, the disease can in most instances be successfully managed from general practice.

References

1. Ehringer H, Hornykiewicz O. Verteilung von noradrenaline und dopamin (3-hydroxytramin) in gemirn des mewschhen und ihr verhalten bei erkankungen des extrapxramidalen system. *Klin Wochenschr* 1960; **38:** 1236.
2. Yahr MD. Pharmacological treatment of Parkinson's disease in early and late phases. In: *Research progress in Parkinson's disease.* Bath: Pitman, 1981: 233-241.
3. Boshes B. Sinemet and the treatment of parkinsonism. *Ann Intern Med* 1981; **94:** 364-370.
4. Hoehn MM. Increased dosage of carbidopa in patients with Parkinson's disease receiving low doses of L-dopa. *Arch Neurol* 1980; **37:** 146-149.
5. Nibbelink DW. Sinemet 25: 100. In: *Research progress in Parkinson's disease.* Bath: Pitman, 1981: 226-233.
6. Godwin-Austen RB, Smith NS. Comparison of the effects of bromocriptine and levodopa in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1977; **40:** 479-482.
7. Rinne UK. Recent advances in the treatment of Parkinson's disease. *Acta Neurol Scand* (Suppl 1) 1980; **78:** 103-121.
8. Teychenne PF, Bergsurd D, Racy A, *et al.* Bromocriptine low dose therapy in Parkinson's disease. *Neurology (NY)* 1982; **32:** 577-582.
9. Anonymous. L-Deprenyl in Parkinson's disease. *Lancet* 1982; **2:** 695-696.
10. Weiner M. Update of anti-parkinsonian agents. *Geriatrics* 1982; **37:** 81-84, 89-91.
11. Rinne UK, Molsa P. Levodopa with benserazide or carbidopa in Parkinson's disease. *Neurology (NY)* 1979; **12:** 1584-1589.
12. Kent S. Assessing L-dopa treatment in Parkinson's disease. *Geriatrics* 1981; **36:** 34-42.
13. White NJ, Barnes TRE. Senile parkinsonism. A survey of current treatment. *Age Ageing* 1981; **10:** 31-36.
14. Franz DW. Drugs for Parkinson's disease: centrally acting muscle relaxants. In: *The pharmacological basis of therapeutics.* New York: MacMillan, 1975: 227-244.
15. Parkes JD. *Parkinson's disease. Update postgraduate centre series no. 8.* London: Update, 1982.

Acknowledgements

I wish to thank the general practitioners at the Clydebank Health Centre for their assistance in preparing this paper.

Address for correspondence

Dr J.A. Wilson, Medical/Geriatric Department, Bangour General Hospital, Broxburn, West Lothian EH52 6LR.