The treatment of Parkinson's disease*

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Summary

The treatment of Parkinson's disease is discussed. Levodopa is the most effective drug in this therapy. The place of other agents is discussed.

Introduction

Advances in the treatment of Parkinsonism over the last decade have significantly improved the morbidity from this condition and also changed the natural history of the disease. These improvements have, of course, resulted from the introduction of a succession of new forms of medical treatment—levodopa, amantadine, decarboxylase inhibitors and finally synthetic dopamine agonists—and it has become difficult for the medical profession always to remain up to date with the latest development. There are problems about when to introduce treatment, what drugs to use in combination, how to treat side effects and what benefits can be expected from any drug combination. In this paper the author attempts to review the current position regarding treatment together with a short discussion of probable advances in the future.

Diagnosis

Of great importance in the treatment of Parkinson's disease is firstly the distinction of symptomatic cases from idiopathic Parkinsonism. It is generally true that symptomatic Parkinsonism responds less well to medical treatment than idiopathic Parkinson's disease. And the patient with Parkinson's disease responds very much better if the disease is uncomplicated by other disease of the nervous system. For example in a study of the effects of age and arteriosclerosis on Parkinsonism (Godwin-Austen, Bergmann and Frears, 1971), it was shown that patients under the age of 65 years, when presumably arteriosclerotic changes are less, did better on treatment with levodopa than did patients above that age; and patients with cerebral arteriosclerosis showed no significant response to such treatment.

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The patient, therefore, has to be assessed at the time of diagnosis and there are three main considerations that apply (Table 1).

TABLE 1. Considerations for assessment of patient at diagnosis

1. Type of Parkinsonism—Primary
—Symptomatic
2. Associated CNS or systemic disease
3. Disability

The associated systemic disorders that are of particular importance are abnormalities of blood pressure, either hypertension or postural hypotension, cardiac arrhythmias, glaucoma and prostaticism. Neurological abnormalities that must be carefully assessed include dementia, active or past psychiatric disorder and cerebral vascular disease either with or without persisting deficit. These conditions may act as partial or absolute contra-indication to some types of treatment or necessitate modification of that treatment. Finally, it is of great importance to assess the severity of the parkinsonian disability and how it affects the individual patient. One patient may be incapacitated by tremor where another has disturbance of balance. And the severity of individual symptoms is an important factor in choosing treatment. The most obvious example of this fact is the selection for surgery of the rare case of uncomplicated unilateral tremor but the features that should be considered at the time of diagnosis are as in Table 2.

TABLE 2. Assessment of disability

1. Independence for washing, feeding, dressing
2. Functional and social significance of tremor
3. Gait/balance disturbance—symptomatic and objective
4. Objective assessment of tremor, rigidity and bradykinesia
5. Salivation, constipation, depression, insomnia, pain

The forms of treatment currently available and their indications and side effects must now be discussed.

Treatment with levodopa

Levodopa remains the most effective drug in the treatment of Parkinson's disease. A considerable

proportion of ingested levodopa is metabolized extracerebrally by the enzyme dopa-decarboxylase so that dopa is now normally administered with an extracerebral decarboxylase inhibitor such as carbidopa (as in 'Sinemet') or benserazide (as in 'Madopar'). It is important to note that no side effects either central or peripheral have yet been attributed to the decarboxylase inhibitor.

The therapeutic effects of levodopa with or without a decarboxylase inhibitor are the same, but the addition of a decarboxylase inhibitor allows for a reduced dose of levodopa, probably a more rapid response, a 'smoother' therapeutic response with less diurnal fluctuation and, most importantly, a reduction in the peripheral side effects of levodopa. Marsden and his co-workers demonstrated (Marsden *et al.*, 1973) the considerable reduction in incidence of peripheral side effects, especially nausea and vomiting, and it is the absence of this side effect that makes 'Sinemet' or 'Madopar' better tolerated over a longer period of time than levodopa alone.

Levodopa is absorbed and metabolized rapidly. Thus it should be administered 3- or 4-hourly and some patients benefit from even more frequent dosage.

The action of levodopa is on all the manifestations of Parkinson's disease but hypokinesia and the resulting functional disability show the greatest response. Rigidity is greatly improved in the majority of patients, and tremor significantly reduced in a minority. Disturbance of gait and of posture may be dramatically relieved. There is seldom much improvement in dysarthria or dysphonia. Using combined preparations the response is rarely delayed more than a few weeks, although it may take time for the patient to learn to take full advantage of the benefits that treatment has produced.

In about 20% of patients the effect of levodopa-containing treatment is dramatic so that there may be scarcely any detectable features of Parkinsonism. In about 50% of patients the improvement, while judged 'moderate' or 'slight', may be sufficient to make the critical difference between independence and dependency.

Dosage should be started low and increased on alternate days or twice weekly until an optimum therapeutic response has been achieved, or side effects develop.

Levodopa should normally be given, in the moderate or severely afflicted case, in association with the second important group of drugs—the anticholinergics. This is because, as Hughes showed in 1971 (Hughes *et al.*, 1971), the anticholinergics have an additive therapeutic action. But whereas levodopa is most beneficial to the hypokinetic patient, anticholinergics have their principal action on rigidity—with lesser effect on tremor. There are many who

believe that the very mildly afflicted patient with slight rigidity and tremor is best treated with anticholinergics alone. Certainly, these drugs have a decreasing margin between therapeutic and toxic effects in the severely afflicted patient on high dosage. There are a large number of these drugs to choose from. The three used by the author are benhexol, orphenadrine and benaprizine.

Side effects of levodopa

Side effects of levodopa and anticholinergics can be separated into peripheral effects of the drugs and central side effects.

The peripheral side effects of levodopa are those which are greatly reduced by the use of a decarboxylase inhibitor. Nausea and vomiting is the most frequent and important such side effect but postural hypotension may occasionally produce severe symptoms. Cardiac dysrhythmias may be caused by levodopa so that any patient with a history of myocardial ischaemia should be treated with a combined preparation of levodopa and decarboxylase inhibitor. Occasional side effects are abnormal sweating, burning paraesthesiae, distortions of taste and abnormal dreaming.

Abnormal movements are the most serious long term side effect of levodopa. They most commonly affect the face and unfortunately the patients showing greatest benefit are most likely to develop this side effect. The movements are usually choreo-athetoid but dystonic spasm, which is frequently painful, may occur. 'On-off' attacks in which the patient may abruptly become akinetic and lose all benefit of treatment for about one hour is another serious side effect experienced by an increasing proportion of patients after periods of treatment for a few months or longer.

Both these side effects are variable during the course of the day and are probably related to the level of cerebral dopamine amongst other factors.

Psychological side effects are most frequently seen in patients who are demented or have a history of psychiatric disturbance. It is therefore important to be aware of any such past history and to treat any pre-existing endogenous depression before starting levodopa.

This description of side effects may leave an impression of dubious advantage for these medical treatments. But this is of course certainly not the case. The advantages far outweigh the disadvantages in the majority of patients and one of the problems of treatment is the patient who, against instructions, increases his dose of levodopa to get greater benefit and thereby makes his abnormal movements worse.

It must be remembered that 'Sinemet' or 'Madopar' must not be given with levodopa because the proportions of inhibitor to levodopa are optimal. And

monoamine oxidase inhibitors for depression are absolutely contraindicated with levodopa because they may cause dangerous hypertensive reactions.

Other agents

Amantadine has a similar range of therapeutic effect to levodopa but its response is very much less. The author uses amantadine as additional treatment in patients who tolerate only sub-optimal dosage of levodopa. It is very well tolerated by most patients although the benefits seem to be greatest when it is first used and decline within 1 to 3 months. Side effects include confusion, restlessness and insomnia.

What is the current role of stereotactic thalamotomy in the treatment of Parkinsonism? The patient with severe unilateral tremor who has failed to respond to medical treatment may be greatly improved symptomatically by thalamotomy. In such cases the risk of morbidity, which is about 5%, is justified. Surgery relieves tremor and has some effect on rigidity. It has no effect on hypokinesia. Gait disturbance, dysarthria and dysphonia may be made worse by surgical intervention especially where bilateral thalamotomy is performed. Dementia, arteriosclerosis, hypertension and incontinence are all contraindications to surgery.

Levodopa and related drugs, anticholinergics and surgery are the specific treatments for the symptoms of Parkinsonism but there are other less specific treatments that are sometimes indicated in addition.

Beta-blockers such as propranolol may be occasionally beneficial in the relief of parkinsonian tremor. Depression is a very common symptom in Parkinson's disease to such an extent that it is regarded by some as part of the syndrome. Tricyclic antidepressants have an anticholinergic effect and are consequently doubly valuable in a patient with significant depression. Excessive salivation may require additional therapy with atropine or probanthine. The treatment of insomnia and constipation is frequently of great importance. Physiotherapy may be of great value in patients who are being started on treatment; it may also be useful in the case with painful complications of immobility. But physiotherapy should be limited to courses lasting up to three months with the patient responsible subsequently for maintaining physical exercise under his own initiative.

Perhaps more important than anything in treating these patients is giving them psychological support and encouragement. Most patients should be told the diagnosis and advised that the disease will not 'go away' nor can it be 'cured'. But it should be emphasized that much can be done for the symptoms both immediately and if the disease progresses. The patient

must of course be encouraged to retain his independence and not allow relatives to help him just to save time. He must retain his interests in hobbies and reading and should be as physically active as possible. An active, hopeful approach is most important in counteracting the depression and lethargy that are so much part of the disease.

The recent history of the treatment of Parkinsonism has been one of rapid change and there is every indication of further advances in treatment in the future. For example synthetic dopa-like drugs are becoming available and the first that is being marketed, albeit for different indications, is bromocriptine. A trial of this drug has recently been completed comparing it with levodopa. In the majority of patients it is less effective even at optimal dosage and the central side effects—confusion and memory disturbance—were worse than with levodopa. However, a few patients tolerated bromocriptine better than they did levodopa and in this trial there were no patients who developed abnormal movements or 'on-off' attacks while on treatment with bromocriptine alone—even where these side effects had been troublesome with levodopa. Bromocriptine is probably the most promising synthetic dopamine agonist currently available but there is no doubt that many other similar compounds will be developed in the near future. The hope is that such drugs will allow the separation of therapeutic effect from central toxic effect and particularly enable us to treat Parkinson's disease without the emergence of the dyskinetic side effects or the 'on-off' reaction.

Similarly there has been recently renewed interest in the potentiating effect on levodopa of synthetic melanocyte-inhibitory factor.

Already improvements in the quality of life and longevity have been achieved by advances in the treatment of this disease which have been introduced during the last ten years. There is every reason to hope that similar advances in the next decade will lead to further improvement in the treatment of this common disabling disease.

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