DRUG THERAPY IN THE MANAGEMENT OF PARKINSON’S DISEASE

PART II

Aims of drug therapy

The aim is to improve mobility and functional capacity (symptomatic control). Parkinson’s disease (PD) is a slowly progressive disorder. Although drugs are usually effective in the early stages, their efficacy is not sustained and, indeed, the long-term complications of treatment may develop with the symptoms of later disease. The extent to which levodopa itself contributes to this is unknown and still very controversial, but such considerations may influence the choice of initial therapy. Levodopa is acknowledged as the mainstay of treatment of PD but attempts to delay its introduction by the use of alternative therapies may be considered in those who have relatively manageable symptoms at presentation. There has been no adequate evidence for drugs slowing the rate of deterioration (neuroprotection).

Influence of age on choice of initial therapy

Reference is made to “younger” and “older” patients in the following text. This should be based on clinical assessment of the individual case taking into account “biological” rather than actual age, cognitive function and life expectancy.

2.0 TREATMENT OF EARLY DISEASE

There are options for treatment. It is important that the decision to treat takes into account the wishes of the patient (and carer, if necessary).

2.1 No therapy meanwhile

... if a decision to delay drug therapy is appropriate. Make the diagnosis, discuss it with the patient but withhold treatment until there is a significant functional disability. This may apply particularly to some of the ‘younger’ patients with ‘mild’ symptoms.

2.2 Levodopa monotherapy

Levodopa is the most effective drug in the treatment of PD and symptoms readily respond in the majority of cases. Unfortunately, motor complications (dyskinesias and motor fluctuations) often begin to develop within five years of treatment and are generally more of a problem in “younger” patients.

Treatment with levodopa should be initiated once the physician and patient/carer agree that functional capacity is impaired.

Grade B, evidence IIb
Levodopa is always administered in combination with a dopa-decarboxylase inhibitor, benserazide (co-beneldopa, Madopar®) or carbidopa (co-careldopa, Sinemet®). It may be taken either as a conventional capsule/tablet or in sustained release (CR) form.

Commence treatment with levodopa dosage in the lower range (e.g. Madopar/Sinemet to provide levodopa 100-200mg daily in 2-3 divided doses) with single dose increments weekly until control is achieved or there are incapacitating adverse effects. Higher doses may be required for patients with disabling symptoms. A typical maintenance dose in early disease is 300-600mg daily in 2-4 divided doses. Nocte doses may be useful for patients with troublesome symptoms in bed.

A ratio of levodopa:dopa-decarboxylase inhibitor of 4:1 is preferred in order to achieve adequate inhibition of peripheral decarboxylase activity.\(^1\)

**Grade B, evidence IIb**

### 2.3 Levodopa delay

Delaying the introduction of levodopa may be possible in patients with “mild” symptoms and “minimal” functional impairment if it is thought that this will eventually delay the onset of motor complications. Alternatives to levodopa in such cases include selegiline and the dopamine agonists.

#### 2.31 Selegiline monotherapy

A neuroprotective action has been proposed based on selegiline’s potential to block the formation of destructive free radicals derived from the oxidative metabolism of dopamine. However, although randomised controlled trials have shown that selegiline delays the emergence of disability and the progression of signs and symptoms of PD in previously untreated patients,\(^2,3,4,5\) it is likely that this is the result of a mild dopaminergic effect. There is no conclusive evidence of a neuroprotective effect. The initial benefit appears to be relatively short-lived\(^6\).

Selegiline monotherapy (if tolerated) may be considered in early disease in “younger” subjects before levodopa is commenced.

**Grade A, evidence Ib**

Past concerns have been expressed over the safety of selegiline when used in combination with levodopa in the treatment of early PD\(^7\). However, follow-up studies have failed to confirm increased mortality among patients treated with combination therapy at this stage\(^8,9\). Until clarification of safety issues is received, patients may wish to discontinue selegiline once levodopa is commenced. Selegiline should be avoided in postural hypotension, in those who experience frequent falls, and in mental confusion and dementia.

Selegiline is available as conventional tablets or, for those who tolerate it poorly, as Zelapar®, a buccal formulation which avoids liver first pass metabolism and possibly, therefore, reduces the generation of toxic metabolites.
2.32 Dopamine agonist monotherapy

Only bromocriptine, lysuride and ropinirole are licensed for monotherapy. The use of bromocriptine in early PD has generally been associated with reduced efficacy and increased adverse events compared to levodopa. The incidence of motor complications has been reduced in patients able to tolerate bromocriptine monotherapy. Similar efficacy has been shown in the few studies which compare other dopamine agonists with bromocriptine. The role of newer agents such as pergolide, cabergoline, pramipexole and ropinirole requires further evaluation.

Dopamine agonist monotherapy may be considered for “younger” patients with mild disease and without cognitive impairment.

*Grade C, evidence IV*

Side effects of the dopamine agonists are similar to those of levodopa and include nausea, vomiting, postural hypotension and psychiatric disturbances. The latter are more likely in elderly or cognitively impaired patients.

Lysuride is a short-acting drug that requires frequent administration and may be difficult to use in early disease. Ropinirole has been shown to produce a lower prevalence of dyskinesias (5%) compared to levodopa (36%), and almost half the patients continued on monotherapy in a 5 year comparative study (presented but not yet published). There was, however, no difference in the activities of daily living.

Both ropinirole and pramipexole are precluded in patients who wish to continue to drive or use dangerous machinery because of recent reports of the sudden onset of sleep.

The newer dopamine agonists should only be commenced under specialist supervision.

2.4 Combination dopamine agonist plus levodopa

It may be possible to commence levodopa in low dosage (less than 500mg/day) when combined with a dopamine agonist to achieve early control of PD while minimising troublesome dose-related levodopa side-effects. This strategy may delay the onset of levodopa-associated motor complications but this remains controversial.

Low dose levodopa and dopamine agonist combination therapy may be appropriate for “younger” patients when a dopamine agonist alone is ineffective and in order to limit levodopa side effects.

*Grade C, evidence IV*

2.5 Role of centrally-acting anticholinergics

This group includes benzhexol, orphenadrine and procyclidine, which in practice may be used in early disease in patients with tremor and/or rigidity.

Centrally-acting anticholinergic drugs have a role in “younger” patients in whom tremor is a particular problem.

*Grade C, evidence IV*

Treatment is best avoided in the elderly who are very susceptible to the anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention) and in whom mental confusion is a frequent occurrence. Treatment is absolutely contraindicated in patients with glaucoma associated with angle closure and in males with prostatism.
References:

11. Montastruc JL, Rascol O, Senard JM, et al. A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson’s disease: a five year follow up. J Neurol Neurosurg Psychiatry 1994;57:1034-1038