Dopamine agonist monotherapy in early Parkinson's disease

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While levodopa therapy for Parkinson's disease is still considered the gold standard, motor complications are significant disadvantages of treatment. Monotherapy with dopamine agonists may present an alternative approach with a reduced likelihood of developing dyskinesias. Further studies are required before a definitive judgment can be made.

Parkinson's disease (PD) is a common neurodegenerative disorder of later life characterized by bradykinesia, tremor, rigidity and postural instability. As overall life expectancy increases in the Western world the prevalence of the disease will increase. Disease progression results in substantial burdens not only for patients with PD but also for their families and for society as a whole. Increased health resource use, poorer quality of life, caregiver burden, disrupted family relationships, decrease in social and leisure activities, and deteriorating emotional wellbeing are all consequences of the disease (Bergamasco et al, 1990).

Introduction of levodopa in the 1960s revolutionized the outlook for sufferers, making significant symptomatic control of the disease possible for the first time. However, it quickly became apparent that levodopa therapy has a number of limitations, most significantly the development of response fluctuations and dyskinesias during the course of treatment. With each year of levodopa therapy 10% of patients will be affected by motor complications such that after 5 years 50% of patients are affected. In patients with an early onset of the disease (<40 years of age) the rate at which motor complications develop is much greater with almost all patients affected after 6 years of treatment. Dyskinesias, in particular, have a marked impact on patients' quality of life (Clarke et al, 2002).

This sub-optimal adverse event profile for levodopa resulted in a search for other therapies for PD. In the 1970s and 1980s ergot-derived dopamine agonists such as bromocriptine and pergolide were investigated and in the latter half of the 1990s non-ergot dopamine agonists such as pramipexole and ropinirole were introduced. Initially these treatments were used as adjuvant therapy with levodopa but more recently attention has focussed on the use of these drugs as monotherapy in early disease with the aim of delaying the introduction of levodopa. Recently, a number of studies have been published that provide support for this potentially important new approach. This article will consider the results of these studies and will evaluate their impact on the treatment of patients with early PD.

SYMPTOMATIC TRIALS WITH DOPAMINE AGONIST MONOTHERAPY

Bromocriptine was the first dopamine agonist to be studied as monotherapy in PD. These studies have been the subject of a Cochrane review (Ramaker and van Hilten, 2000). The authors concluded that although many of the studies were small or inadequately designed there was still evidence that bromocriptine monotherapy delayed the onset of dyskinesias compared with levodopa therapy, although motor fluctuations were not reduced. Two small studies with lisuride produced similar findings (Rinne, 1989; Allain et al, 2000).

In studies with the more recently introduced dopamine agonists significantly fewer motor complications have been observed compared with levodopa treatment, although there has been some evidence of reduced efficacy and tolerability.

The Parkinson Study Group trial (Parkinson Study Group, 2000) compared the efficacy and tolerability of pramipexole and levodopa over a 2-year period in 301 patients with early PD. Dyskinesias occurred in 10% of the pramipexole group compared with 31% of the levodopa group (hazard ratio (HR) = 0.33; 95% confidence interval (CI) = 0.18–0.6; $P<0.001$).

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However, the mean improvement in total Unified Parkinson's Disease Rating score (UPDRS) from baseline to 23.5 months was greater in the levodopa group compared with the pramipexole group (9.2 *vs* 4.5 points; $P<0.001$). More patients experienced somnolence with pramipexole (four patients in this treatment arm withdrew from the study for this reason compared with only one in the levodopa arm), although the all-cause withdrawal rate was similar in both groups (15% pramipexole and 13% levodopa). Taken as a whole, the authors concluded that the benefits of reduced incidence of dyskinesias with pramipexole treatment outweighed the reduced improvement in UPDRS score and the excess adverse events.

Recently, the results of a long-term follow-up of the pramipexole study have been published in abstract form (Parkinson Study Group and Holloway, 2002). These data indicate that, over a 4-year period, reduction in the risk of developing any dopaminergic motor complication with pramipexole treatment is maintained (52% *vs* 74%, HR = 0.48; 95% CI = 0.35–0.67; $P<0.001$). This was attributable to a significant reduction in dyskinesias (25% *vs* 54%, HR = 0.38; 95% CI = 0.25–0.57; $P<0.001$) with no difference in the prevalence of fluctuations. Despite the opportunity for open-label levodopa supplementation, a greater improvement in UPDRS score was still seen in subjects initially assigned to levodopa compared with subjects initially assigned to pramipexole. Apparently there were more withdrawals from the pramipexole arm (45% *vs* 33%, R Holloway, personal communication, 2002).

In a double-blind 5-year study comparing ropinirole and levodopa in 268 patients with early PD, the cumulative incidence of dyskinesia regardless of levodopa supplementation was 20% in the ropinirole group and 45% in the levodopa group (HR for remaining free of dyskinesia in the ropinirole group = 2.82; 95% CI = 1.78–4.44; $P<0.001$; Rascol et al, 2000). The two groups were not significantly different in the mean change in UPDRS scores for activities of daily living but there was a significant difference in motor scores in favour of the levodopa group (adjusted treatment difference = 4.48 points; 95% CI = 1.25–7.72; $P=0.008$). Adverse events led to the early withdrawal from the study of 27% of the patients in the ropinirole group and 33% of patients in the levodopa group. Hallucinations were significantly more common with ropinirole. Overall withdrawal rates after 5 years were 47% from the ropinirole arm and 51% from the levodopa arm.

Cabergoline monotherapy in patients with newly diagnosed PD has been compared with levodopa monotherapy as part of a 5-year study in 412 patients. The results of this study are only available in abstract form (Rinne, 1999). Both treatments improved motor disability while the development of motor complications was significantly less frequent in patients receiving cabergoline compared with those receiving levodopa (22% *vs* 34%; $P<0.02$). Similar withdrawal rates (16% cabergoline, 13% levodopa) were observed in both treatment groups.

The pergolide *vs* levodopa monotherapy trial involved 294 patients with PD over 3 years. It too has only been published in abstract form (Oertel, 2000). It differed from the other three trials in that open-label 'rescue' levodopa was not allowed. After 3 years, 16% of those randomized to pergolide had motor complications compared with 33% of those treated with levodopa; no statistical comparison is available. However, levodopa produced greater improvement in UPDRS motor scores than pergolide. More withdrew from treatment with pergolide than levodopa because of adverse events (18% *vs* 10%).

HOW RELIABLE AND GENERALIZABLE ARE THE RESULTS OF THE SYMPTOMATIC STUDIES?

Most of the trials performed with dopamine agonists as monotherapy have been relatively short. Even the so-called long-term studies with pramipexole and ropinirole have lasted only 3–5 years, a comparatively short term in the treatment of patients with PD. Results from studies in patients followed up over a period of 5–10 years are required before the long-term value of dopamine agonist monotherapy compared with levodopa therapy can be truly assessed.

Most studies have recruited comparatively young patients (mean age around 60 years). While this is advantageous in assessing the value of dopamine agonist monotherapy in this age group there is currently insufficient information upon which to judge the value of this therapeutic strategy in the vast majority patients with PD who are generally much older than this.

Furthermore, measurements of quality of life and health economics have not been performed in the studies conducted so far, making it impossible to assess the effectiveness and cost effectiveness of treatment.

It is clear that there are many outstanding questions that will only be answered by further studies. The PD MED trial which is currently in progress in the UK should provide such answers.

This study will recruit approximately 1500 early PD patients and a further 1000 patients with later disease. Among the questions that the study has set out to answer is whether or not dopamine agonist monotherapy delaying the onset of motor complications has a beneficial effect on quality of life and whether this is cost effective (http://www.pdmed.bham.ac.uk/).

IMAGING STUDIES WITH DOPAMINE AGONIST MONOTHERAPY

Recently, dopamine transporter imaging using single-photon emission computed tomography (SPECT) with 2β-carboxymethoxy-3β(4-iodophenyl) tropane (β-CIT) labelled with iodine-123 has been used to assess the progression of dopamine neuronal degeneration in PD. In a sub-study of the pramipexole trial considered above the effects of initial therapy with pramipexole on change from baseline in the uptake of [^{123}I]β-CIT was compared with initial therapy with levodopa at 22, 34 and 46 months after commencing treatment (Marek et al, 2002). Patients receiving pramipexole showed a marked reduction in loss of [^{123}I]β-CIT uptake compared with those receiving levodopa over the 46-month period (7.1% pramipexole *vs* 13.5% levodopa, P=0.004 at 22 months; 16.0% pramipexole *vs* 25.5% levodopa, P=0.01 at 46 months).

In a similar study of ropinirole treatment over a 2-year period, the extent of dopamine neuronal degeneration was assessed using three-dimensional positron emission tomography (PET) to measure the putamen uptake of ^{18}F-fluorodopa. Only the results presented at a recent conference are currently available but these show that the loss of putamen ^{18}F-fluorodopa uptake was significantly slower with ropinirole compared with levodopa (–13% ropinirole *vs* –20% levodopa; P= 0.022) (Whone et al, 2002).

KEY POINTS

- Motor complications in Parkinson's disease are a consequence of levodopa therapy.
- Clinical trials have shown that dopamine agonist monotherapy results in fewer motor complications than levodopa.
- Agonist monotherapy is not as effective in treating motor impairments and disability and causes an excess of adverse events compared with levodopa.
- Recent imaging studies suggest that agonist monotherapy may slow the degeneration of dopaminergic neurones and/or that levodopa is toxic but this work has been criticized.
- Large-scale clinical studies are now required to assess the effectiveness and safety of dopamine agonist monotherapy.

The authors of both studies interpret these results as dopamine agonist monotherapy resulting in a significantly slower rate of loss of dopaminergic neuronal function compared with levodopa, either because the agonists are neuroprotective, levodopa is toxic or both. However, this work has been criticized on a number of grounds (Morrish, 2002). Do these two surrogate markers really measure the number of remaining dopaminergic neurones? An alternative explanation may be that the agonists and levodopa have differential pharmacological effects on the dopamine transporter and fluorodopa uptake. In the pramipexole study, the improvement in UPDRS score in the SPECT sub-set was as great in the pramipexole group as it was in the levodopa group. This is in contrast with the whole trial population in which the pramipexole group fared worse than the levodopa group in terms of the improvement in UPDRS. This raises the possibility that the pramipexole sub-set in the SPECT trial were, by chance, slow progressors.

Further work is required on the potential protective effects of agonists and the possibility that levodopa is toxic. Large pragmatic trials, such as PD MED, are required to examine mortality after long-term follow-up of patients randomized to agonists or levodopa.

CONCLUSIONS

There is now a large body of evidence showing that dopamine agonists can be used successfully as monotherapy in the treatment of early PD. It is clear that treatment with dopamine agonists reduces the risk of developing dyskinesias. Benefit appears to be maintained for at least 3–5 years.

Recent results raise the possibility that the non-ergot-derived dopamine agonists ropinirole and pramipexole may exert a neuroprotective effect, slowing the rate of dopaminergic degeneration when used in the early treatment of patients with PD, and/or that levodopa may be neurotoxic. More work is required to confirm this before practice is changed on this basis.

However, while agonist monotherapy results in fewer motor complications than levodopa and may be neuroprotective, patients experience an excess of other adverse effects such as somnolence and confusion. They also experience a reduction in efficacy compared with levodopa monotherapy.

Clearly, significant uncertainty surrounds the available clinical evidence. So, which patients with early PD should be given dopamine agonist monotherapy if they are unwilling to accept randomization into a clinical trial such as PD

MED? The existing trial evidence applies mainly to younger patients with PD. In such patients the evidence suggests that agonist monotherapy is an appropriate choice. For the vast majority of older PD patients, there is insufficient trial data to draw any firm conclusions and such patients are better entered into a trial or the current uncertainties will continue ad infinitum. **HM**

Conflict of interest: Dr Clarke has received payment from the manufacturers of most of the drugs discussed above for consultancy work, lectures and travel expenses.

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