EDITORIAL

The initial drug treatment of older patients with Parkinson’s disease – consider an agonist, but don’t demonise dopa

The widening array of drugs available for treating people with Parkinson’s disease (PD) raises several questions, e.g. when should the newer drugs be used, and what now is the place of levodopa in older patients?

Originally introduced as an adjunct to levodopa when the latter lost its efficacy, evidence is now accruing that early direct dopaminergic agonist monotherapy as an alternative to levodopa reduces motor complications. Similar findings were seen in studies with the two synthetic agonists – ropinirole (Requip®) [1] and pramipexole (Mirapex®) [2] and also with the ergoline, pergolide (Celance®, Permax®) [3]. Each showed slightly less efficacy than levodopa in relieving symptoms (as evidenced by the UPDRS) but with the major long-term advantage of a reduction of motor complications by about half. In addition, imaging studies suggest that the disease course may be changed [4, 5] and there is evidence that this may result from the decreased use of levodopa [6]. Is this evidence robust enough to advocate a radical change of practice in older patients?

Some caution has to be exercised when extrapolating these results to older people as the average age of patients was only around 63 years, and all the studies excluded patients with cognitive impairment. Older patients experienced a higher rate of side-effects, including hallucinations, orthostatic hypotension, somnolence and oedema. Age alone, however, is not a contraindication to agonist monotherapy, and several studies have demonstrated reasonable tolerance in well-selected octogenarians [7].

Levodopa nevertheless remains the most effective and appropriate option for patients in whom a rapid response is required, or if agonists are contra-indicated (e.g. because of concomitant diseases, particularly cardiovascular problems or cognitive impairment).

The patient and relevant family should therefore be informed that there are choices to be made about the different treatments, and they should be involved in the decision, which will take factors such as co-morbidity, concomitant medication, and patient expectations into account [8]. Most patients will require levodopa at some stage, albeit at a lower dose, so we should avoid demonising this drug to prevent undue distress when it is required later.

With a life expectancy even for sexagenarians of 15–20 years the choice of initial treatment may be critical, and it is sensible to offer the patient the chance of avoiding motor complications. Because of the long-term consequences of l-dopa therapy the guidelines now recommend that its initiation should be delayed as long as possible, provided that adequate relief can be achieved with other treatment strategies [8–10]. They should be supervised by those experienced in their use, and aware of practical issues and side-effects. The two newer dopamine agonists, pramipexole and ropinirole, in contrast to the ergolines, have not caused pleural, pulmonary or retroperitoneal fibrosis. All require a careful titration to full dose, and domperidone cover is required by some patients who are sensitive to their emetic effect.

When the initial treatment has nevertheless been a levodopa preparation, the prescriber is advised to keep the dose as low as possible. If doses of 300–500 mg have been reached, and are starting to prove ineffective, the choice lies between enhancing the effect of dopa either by adding a catechol-O-methyl transferase (COMT) inhibitor (entacapone), or a monoamine oxidase inhibitor (selegiline), or starting a direct agonist as an adjunct. In addition, if not already under the care of a specialist team, the patient should be referred to one since this stage represents the beginning of the complex phase of PD [11], and other disease-related problems are likely to appear.

In adjunctive therapy dopamine agonists have demonstrated levodopa’s sparing effects with increased ‘on’ time. Their longer action (half-life of cabergoline is over 60 h) offers very real continuous dopaminergic stimulation, but in the older patient there is the continued risk of side-effects.

With the routine use of levodopa accompanied by peripheral dopa-decarboxylase inhibitors COMT becomes mainly responsible for levodopa’s breakdown. Entacapone inhibits this enzyme improving ‘on time’ and should be considered as soon as the patient is aware of ‘wearing-off’ (i.e. when each dose of levodopa lasts a shorter period of time), necessitating more frequent dosing.
In contrast to tolcapone (Tasmar\textsuperscript{2}), the prototype that was withdrawn following three deaths from liver toxicity, entacapone needs no routine LFT monitoring. Its side-effects are primarily those of levodopa, the dose of which should be reduced. It also causes orange staining of the urine about which patients should be warned. The manufacturers advise that each dose of levodopa should be accompanied by 200 mg entacapone, although many clinicians prefer to initiate it more gradually.

Selegiline is a monoamine oxidase inhibitor (type B) that selectively inhibits the oxidative metabolism of levodopa and endogenous dopamine. Several controversies surround its use. A single study from the UK suggested an increased mortality in combined use with levodopa. Other studies failed to corroborate this, but it is now widely agreed that it should be avoided in the presence of postural hypotension, dementia or psychosis, and general frailty. Conventionally 10 mg is taken in the morning to avoid insomnia from its amphetamine metabolites, but a recent option is the buccally absorbed 1.25 mg preparation (Zelapar\textsuperscript{3}) that reduces amphetamine metabolites and has more predictable pharmacokinetics [12].

Neither amantadine nor anticholinergics (antimuscarinics) are generally prescribed in older patients because of their frequent side-effects although amantidine is enjoying resurgence as an anti-dyskinetic agent.

In summary, careful prescribing can enhance the quality of life of patients with PD, and also that of their carers. In de novo cases an agonist should be considered before resorting to levodopa, but in recognition of the inevitable progression of the disease and the continued utility of levodopa, it would be unwise to demonise the latter in this process.

References