The treatment of Parkinson’s disease has always been controversial.

IS DOPAMINE BAD?

There is a long history of concern that dopamine itself may be neurotoxic, but this has been largely put to rest, and in fact one interpretation of the recent ELLDOPA study is that dopamine may be neuroprotective. In this study patients with early-onset PD were placed on either placebo or various strengths of dopamine, ranging from 150 mg to 600 mg daily. To everybody’s surprise, at the end of the study when the drugs were withdrawn, the group of 600 mg daily did not deteriorate to baseline and the group of placebo remained significantly worse. The most parsimonious interpretation of this is simply that the wash-out period was not long enough and that dopamine has effects which last much longer than 2 weeks. However, if dopamine were to be newly released on the market, it might well be hailed as the newest and the best form of neuroprotection available: there is certainly no evidence that dopamine adversely affects disease progression.

WHAT IS THE TREATMENT OF CHOICE FOR NEWLY DIAGNOSED PD?

Overview

Frequently, algorithms and practice guidelines suggest that the drugs of first choice in the treatment of PD should be dopamine agonists. The reasoning underlying this recommendation is the concern that early use of dopamine is associated with the development of fluctuations and dyskinesias. Dopamine agonists available in South Africa include the following: bromocriptine (Parlodel), pergolide (Permax) and newer agonists such as ropinerole (Requip) and pramipexole (Pexola).

To some extent the background history of the recommendations reflects the ease of developing an animal model induced by the chemical MPTP and the rapid (within weeks) development of dyskinesias and fluctuations in these models. Another piece of the jigsaw puzzle is the theory which, although likely to be correct, remains unproven, namely that either constant levels of dopamine or other dopamine receptor-stimulating agents are more likely to be of benefit to patients than intermittent dopaminergic stimulation.

The fundamental underpinning of problems such as fluctuations and dyskinesias in PD reflects the progression of illness and relentless loss of dopaminergic neurones and, in particular, loss of functional storage capacity of these neurones. In the extreme case, in the virtual absence of any dopaminergic neurones, normal basal ganglia function becomes entirely dependent on dopamine from an external source. By contrast, early on in the disease, with a relatively large number of surviving neurones and relatively good storage capacity, patients will often have virtually normal motor function throughout the day. With progression of disease and progressive loss of storage capacity, there is increasing evidence of the short half-life of dopamine, and patients will start to experience the phenomenon of ‘wearing off’, where their dose clearly lasts a shorter time than it had before. Subsequently many of these patients will go on to develop clear motor fluctuations. Fluctuations largely consist of changes in the motor state, and hence are often referred to as on and off phenomena, reflecting good and impaired motor function respectively.

What are dyskinesias and are they important?

Dyskinesias are involuntary movements, often of a choreiform nature. They are frequently complex, particularly in their relationship with the level of dopamine in the basal ganglia. Common patterns include dyskinesias restricted only to the off-state, dyskinesias restricted only to the on-
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state (peak-dose dyskinesias) and dyskinesias which occur as the clinical state moves from off to on and again from on to off. Treatment of dyskinesias can be difficult and taxing for both patient and neurologist.

In the ideal situation, constant stimulation of dopaminergic receptors may result in less fluctuation and fewer dyskinesias. Indeed, a number of trials have clearly shown that using dopamine agonists delays the development of dyskinesias. Delay in development of dyskinesias is the major reason that dopamine agonists are often held to be the agent of first choice in the patient with newly diagnosed PD.

An important question is, ‘how common are dyskinesias?’ A review of the current literature indicated that slightly less than 40% of patients will develop dyskinesias after 4-6 years of dopamine treatment. A community study based at the Mayo Clinic has shown that dyskinesias are relatively uncommon in the elderly, with an incidence of 16%. Compared with this group, patients who had PD that started between the ages of 40 and 59 years had an incidence of dyskinesias of 50%. The authors of this study concluded ‘these data suggest that troublesome dyskinesias are not a high risk among PD patients in the community, and many may be completely spared’. It is important to note that although figures vary, the usual age of onset for PD is in the early sixties, and thus the majority of PD patients have substantially less risk for developing dyskinesias than do young-onset PD patients.

An additional question is related to the severity of dyskinesias. Many studies have reported a high incidence of dyskinesias, but these are frequently relatively trivial for the patient, and can be improved by minor adjustments of medication. Reviewing the quality of life in early PD, motor complications (fluctuation and dyskinesias) were not important in the first 4 years of treating PD.

How much dopamine agonist do you need to prevent dyskinesias developing?

It is important to realise that the dose of dopamine agonist is not trivial: daily doses of 16.5 mg of ropinirole were given in the study of Rascol et al., 12 mg daily in the REAL-PET study, and 2.8 mg daily of pramipexole in the CALM-PD study.

Which is better – dopamine or dopamine agonists?

In general, dopamine agonists are likely to be less effective, have a worse side-effect profile and are expensive. What is critical about guidelines suggesting that dopamine agonists be the first line of treatment for PD is that all studies have shown that the beneficial effect on motor function of dopamine agonists is significantly worse than that of dopamine itself: therefore in the REAL-PET study, the mean UPDRS (a rating scale for PD function) score change from baseline showed a significantly greater improvement with levodopa compared with the agonist: improvement of 5.6 versus a decline of 0.7 (CI 3.5 - 9.1). Similarly, in the CALM-PD study motor UPDRS scores had a difference of 5 (< 0.001).

One reason for patients to have developed less dyskinesia in these studies is simply that they were treated with less potent medicine. Finally, as with many conditions where there are valid arguments to be made on both sides, the final result may not be all that different, and it is worth noting that in the initial study on the effect of dopamine agonists on dyskinesia incidence, by the end of 5 years two-thirds of the patients on dopamine agonists required the addition of supplementary levodopa.

On theoretical grounds, dopamine agonists with longer half-lives may be better than those with shorter half-lives, and the clinician should be aware of the existence of 2 dopamine agonists that may prove useful, both with long half-lives, namely the drug rotigotine, which has been quite widely tested in South Africa in phase 3 trials in the form of a topically applied patch, and the dopamine agonist, cabergoline, which is available in South Africa for the reduction of lactation.

Who must get dopamine agonists as first-line treatment?

Young-onset PD patients are particularly prone to dyskinesias, and it seems sensible that they should start with a dopamine agonist if possible. However, younger patients will inevitably require surgery for severe dyskinesias, and patients should not be denied the greater efficacy of dopamine if they are not responding well to dopamine agonists, particularly if their livelihood is affected.

The definition of young onset is naturally an arbitrary one: for the purpose of deciding whether to give dopamine agonists or not, the usual age given is 50 years. Neurologists may well decide that patients aged 50-60 may also fall into a higher risk category for developing dyskinesias, although their risk is lower than for younger patients.

What other drugs are available as first-line treatment?

Other agents available as first-line treatment include:
- Anticholinergics, which are probably

particularly useful in the control of
tremor. There are significant concerns about
long-term use of anticholinergics and their use in the elderly needs
to be viewed with caution, particu-
larly since they potentially cause
dementia.
• Amantadine, which has benefit,
but typically for a short dura-
tion only.
• Selegiline and rasagiline.

NEUROPROTECTION IN PD

The Holy Grail in PD is unquestionably
the development of neuroprotection
to prevent damage to cells from
accumulating injury. Currently the
treatment of PD is purely symptomatic
and there are no proven forms of
neuroprotection.

Drugs which have been closely
associated with neuroprotective
strategies include monoamine
oxidase inhibitors, antioxidant, such as
selegiline and, more recently, rasagiline. The idea behind these
agents is once again derived from
animal models of PD, in which
selegiline was successfully able to
counter the effects of the mitochondrial
toxin, MPTP. It is reasonable to
ask whether this animal model is a
good one (opinions differ) and how
important mitochondrial dysfunction is
in PD (opinions differ).

Selegiline was tested in the DATATOP
study and appeared to delay the
progression of PD.10 The fly in the
ointment was that drugs which block
monoamine oxidase are likely to
lead to direct symptomatic benefits
and elucidating whether there is an
additional neuroprotective aspect over
and above the direct symptomatic
benefit derived from MAOI treatment
is difficult. A similar effect is seen with
rasagiline.11

Although a neuroprotective study
has been carried out, and may show
benefit, the study design is novel, and
interpretation of the potential benefit of
rasagiline as a neuroprotective agent is
difficult.12

Virtually all drugs associated with
the treatment of PD are also thought
to potentially have neuroprotective
function: this would include dopamine
agonists and COMT inhibitors.
Although studies using dopamine
agonists (REAL-PET and CALM-PD)
have had imaging findings suggestive of
neuroprotection, this did not reflect
an improvement in motor benefit, and
the imaging findings were possibly
related to different effects on imaging
parameters, rather than actual
neuroprotection.4,6

WHAT IS THE ROLE OF
STEM-CELL THERAPY FOR
PD?

Principally, stem-cell therapy can
be viewed as tackling 2 arms of
PD – firstly, the neuroprotective arm
and, secondly, the symptomatic arm.
It is critical to realise that PD is a
progressive illness in which a number of
monoaminergic systems as well as
other, predominantly brainstem,
systems are disrupted. Prominent
symptoms of PD sufferers include
conditions such as altered speech,
cognitive impairment, autonomic
dysfunction and disorders of gait and
balance, the majority of which will
often respond poorly to dopamine
replacement and are therefore likely
to represent dysfunction of non-
dopaminergic systems. Therefore,
stem-cell therapy that is directed
only at dopaminergic neurones is
unlikely to be successful. Where stem
cells may be more promising is in
the field of neurotransaptic factors
and neuroprotection. Trials which have
been at least technically successful
have already been performed
using agents such as a glial-derived
neurotrophic factor. In addition, current
trials are aimed at elevating inhibitory
neurotransmitters in the subthalamic
nucleus, based on the concept that
excessive excitation of cells may result
in cell death.

SURGERY IN PD

Given that PD is a progressive
disorder, it is reasonable to enquire
whether surgical procedures are useful,
given that they are largely palliative.
Unfortunately the situation is clouded
by the fact that there are a number of
different procedures with variable
anatomical sites and variable methods
of achieving the desired result.
However, there is good evidence
that pallidotomy and subthalamic
nucleus (STN) deep brain stimulation
are efficacious as adjutantive therapy,
and are likely to be efficacious in the
treatment of motor complications.13

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