Introduction

The management of idiopathic Parkinson’s disease is deceptively simple. Current practice, which consists of replacing dopamine on a twice or thrice daily regime may actually be responsible for causing the involuntary movements (dyskinesias) which were formerly thought to be inevitable in the disease and which occur in association with levodopa administration. These dyskinesias are usually choreiform, but may also be dystonic or even ballistic. This paper hopes to examine the evidence advocating continuous stimulation of the dopaminergic receptors by means of more frequent dosing of levodopa. Finally, it advises physicians to initiate therapy with a non-ergot dopa agonist in the young and mentally alert, in order to delay the development of dyskinesias. In elderly patients, treatment with levodopa 4 to 5 times a day, in order to achieve continuous dopaminergic stimulation, is recommended.

Historical Perspectives

In 1817, James Parkinson wrote “An Essay on the Shaking Palsy” which aptly described the clinical manifestations of the disease which later bore his name.

Parkinson’s description of “involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellect being uninjured” highlighted a disease entity which had hitherto “escaped particular notice”, and which must have afflicted people much earlier. Four decades after Parkinson’s essay was published, Jean-Martin Charcot added rigidity to the list of symptoms in Parkinson’s excellent clinical description and attached the name Parkinson’s disease (PD) to the syndrome. Treatment of the disease, however, remained largely unsatisfactory.

Therapeutic Strategies

Parkinson had reported efficacy in treatment with opium, but treatment of the disease was largely unsatisfactory through the 19th century. In the 1950s, Artane (trihexyphenidyl), an anticholinergic agent, was used to treat the drooling that was common in the disease, and was found to be efficacious in ameliorating the rigidity and...
tremors as well. This led to its use in the treatment of PD. It soon became obvious, however, that anticholinergics were not robust antiparkinsonian agents. Currently, its primary use is in the treatment of dystonia and the extrapyramidal effects of antipsychotic agents, and it has fallen out of favour in the treatment of PD. The precise mechanism by which anticholinergics act in PD is not known, though a balance between dopaminergic and cholinergic neurotransmission in the basal ganglia has long been believed, and anticholinergic therapy might restore the imbalance resulting from dopaminergic loss. Also, striatal cholinergic interneurons are known to bear D1 and D5 dopamine receptors. Though small in number, they have many synaptic interconnections, thus having the ability to exert effects on medium spiny strial neurons.

In the mid-20th century, Ehringer and Hornykiewicz were credited with highlighting dopamine deficiency in the striatum of patients with Parkinson’s disease, but Tretiakoff had recognised the loss of dopamine-containing cells in the substantia nigra as early as 1917. This association of the disease with dopaminergic cell loss led to the publication, one year later, of positive open-label trials of levodopa given to patients afflicted with Parkinson’s disease in Vienna and Montreal. This breakthrough reduced mortality and provided clinical benefit to virtually all patients. In addition, it was noted that treatment of patients with peripheral decarboxylase inhibitors prior to administration of levodopa markedly intensified and prolonged the “anti-akinesia” effect.

Patients on chronic levodopa therapy reported adverse effects however, among which were mental aberrations, nausea and involuntary movements. Strategies to improve the benefits seen with levodopa soon began in earnest. Inhibition of peripheral dopa-decarboxylase was confirmed to potentiate the effect of levodopa. This had an added benefit – Cotzias soon found that co-administration of levodopa with a peripheral dopa-decarboxylase inhibitor reduced the required dose of levodopa, and attenuated nausea and anorexia. Soon, commercial preparations of levodopa with carbidopa (Sinemet) and benserazide (Madopar) became available.

Other drugs were, however, also known to confer benefit in PD. Dopamine agonists (DA), in the form of apomorphine, had been synthesised from morphine in the 19th century. Weill is credited with having suggested its use as early as 1884 for parkinsonism after noting beneficial results in a patient with Sydenham’s chorea. In 1951, predating the trials with levodopa, Schwab et al reported that apomorphine injections brought about a short-lived but significant improvement in patients with PD. In the 1960s, ergot-derived DAs such as bromocriptine were developed as prolactin inhibitors. In 1967, Fuxe demonstrated the reduced dopamine turnover in hypothalamic and nigrostriatal dopaminergic neurons. This led to studies on the potential use of DAs when levodopa was found to be associated with adverse effects in the form of dyskinesias, motor fluctuations and neuropsychiatric manifestations. Cotzias demonstrated benefit with apomorphine in 1970, but this was associated with problems, prominent among which were the need for parenteral administration and side effects, including nodules and ulcerations at the site of injection. Bromocriptine was soon shown to be efficacious in a double-blind study on 20 patients who were already receiving levodopa. It was soon used routinely in the treatment of PD, and other ergot and non-ergot-derived DAs were subsequently developed and used.

Amantadine, an antiviral agent, was serendipitously discovered to have anti-parkinsonian action in 1969, improving akinesia, rigidity and tremors. Though not well established, postulates of mechanism of action include increasing dopamine release, blocking dopamine reuptake, stimulating dopamine receptors and possibly anticholinergic effects. It has been a commonly held belief that amantadine confers transient benefit, but this is not a universally held view, and many physicians believe that clinical benefits achieved can be sustained. Amantadine is associated with the side effects of confusion, hallucinations, insomnia, and nightmares, especially in the elderly, as well as livedo reticularis, pedal oedema, dry mouth and blurring of vision. Gradual rather than sudden withdrawal of amantadine is advocated, as a sudden cessation of therapy is known to cause dramatic worsening of PD. Amantadine is thought to have N-methyl-D-aspartate (NMDA) antagonist activity, which has led to the belief that it may have neuroprotective properties. In line with work by Chase and Oh, NMDA antagonists such as amantadine are now being used to treat PD patients with dyskinesias.

Dopamine is metabolised by the enzymes monoamine oxidase (MAO) and catechol-O-methyl-transferase (COMT). MAO acts centrally, and COMT both centrally and peripherally. Strategies emerged to reduce the peripheral degradation of levodopa peripherally as well as centrally. Selegiline, a MAO B inhibitor, has been shown to provide symptomatic benefit in patients with PD, although its present role is more as a neuroprotective agent as a result of the DATATOP study. Selegiline fell out of favour after a report from the United Kingdom reported increased mortality in patients treated with selegiline plus levodopa compared to levodopa alone, but this study has been criticised for statistical and methodological flaws, and studies since have not reported increased mortality. Recently, rasagiline, an irreversible MAO-B inhibitor, was shown to improve symptoms of early PD, and promises to modify the progression of the disease.
Despite the administration of levodopa with peripheral dopa-decarboxylase inhibitors, peripheral COMT still metabolises it to the inert metabolite 3-O-methyl-dopa (3-OMD), so that only 10% of a given dose reaches the brain intact. Furthermore, 3-OMD competes with levodopa for transport into the brain via the large neutral amino acid pathway. Following rat studies, Fahn proposed that the combined use of levodopa plus a COMT inhibitor be trialled in humans. Two drugs, tolcapone (Tasmar) and entacapone (Comtan), have been introduced into the market as adjunctive therapy to levodopa and dopa-decarboxylase therapy. Tolcapone acts to inhibit both central and peripheral metabolism of levodopa, but entacapone is a purely peripheral COMT inhibitor. Double-blind, placebo controlled trials have demonstrated the clinical efficacy of both tolcapone and entacapone in that they increase “on” time, decrease “off” time, and improve motor scores in patients with motor fluctuations. Motor fluctuations, as the name implies, describe periods in which patients experience off states, in which the motor features of bradykinesia, tremor and hypokinesia predominate due to wearing off of medications, and on state, with amelioration of these features. Unfortunately, tolcapone was associated with 3 deaths from hepatotoxicity, which prompted its withdrawal from use in many countries. To date, no hepatotoxicity has been demonstrated with entacapone, obviating the need for liver function testing. Figure 1 summarises the therapeutic strategies in the treatment of PD.

Motor Fluctuations and Dyskinesias

Most patients with Parkinson’s disease (PD) can be expected to develop dyskinesias, or involuntary movements, within 5 years of starting levodopa therapy. Poewe and Wenning state that regardless of dose regimens, between 50% and 100% of patients treated with levodopa for more than 5 to 6 years will develop response fluctuations and dyskinesias.

Young-onset PD patients who develop PD between the ages of 21 to 40 are more susceptible to the development of these motor complications, the median interval to developing dyskinesias and motor fluctuations being 3 years compared to 4 and 6 years respectively in older onset (onset after 40 years of age) patients. However, levodopa is not the only culprit. Other antiparkinsonian medications can likewise cause the development of dyskinesias. DAs and anticholinergic medications have been reported to cause dyskinesias. Likewise, catechol-O-methyl-transferase (COMT) inhibitors and MAO B inhibitors have been reported to cause or augment dyskinesias when combined with levodopa. Clearly, then, the development of dyskinesias in PD is not drug-specific.
periods, when the levodopa benefit “wears off” prior to the next dose, with the result that the parkinsonism worsens.\(^2\) Thus, patients with PD may experience freezing episodes, delayed “on” response, dose failures and end-of-dose “wearing off”.

These unbuffered fluctuations in the plasma concentration of short-acting levodopa may impact directly on the striatum, with the result that striatal dopamine receptors are exposed to alternating high and low levels of striatal dopamine. This pulsatile stimulation of the striatal dopamine receptors is now thought to be a key factor in the development of the levodopa-associated motor complications of Parkinson’s disease,\(^2\) through induction of changes in striatal neuronal plasticity, dysregulation of genes and proteins, and alterations in neuronal firing patterns.\(^30\) Consistent with this hypothesis of pulsatile stimulation predisposing to motor fluctuations are observations that the half-life of the dopaminergic agents and disease severity (i.e., degree of nigrostriatal cell loss) are important factors in the development of motor fluctuations and dyskinesias.\(^31-33\)

Intuitively, it would seem to follow that a less pulsatile mode of administration of dopaminergic stimulation would decrease the incidence of these motor complications.\(^34\) Quinn et al.\(^35\) administered continuous intravenous infusion of levodopa to patients with complicated response fluctuations with oral treatment, who had a prolonged and stable clinical response. Long-acting DAs have been shown in animal studies\(^36\) to delay the development of dyskinesias, whereas short-acting DAs do not have the same salutary effect.\(^37\) Prospective double-blind clinical trials in PD patients have likewise shown that initiation of therapy with a long-acting DAs such as ropinirole\(^38\) is less likely to induce motor complications than with the short-acting regular formulation of levodopa.

Levodopa is, however, the most effective anti-parkinsonian medication. As such, any measure to increase its elimination half-life would allow for less pulsatile dopaminergic stimulation. Administration of COMT inhibitors such as entacapone with levodopa in previously untreated MPTP-lesioned monkeys showed enhanced efficacy and reduced frequency of dyskinesias, compared to those treated with levodopa alone.\(^39\) In another study, levodopa was administered twice a day to MPTP-lesioned monkeys, inducing dyskinesias, irrespective of whether it was administered with entacapone. On the other hand, when the same total dose was divided into 4 doses, adding entacapone enhanced motor performance with less dyskinesias compared to levodopa alone.\(^39,40\) This would suggest that smoother delivery of levodopa (i.e., with more frequent administration of levodopa) to PD patients would likewise bring about improvement in motor performance without inducing dyskinesias.

Clinical trials in humans are underway. There is reason to believe that continuous dopaminergic stimulation might also provide benefit in reducing established dyskinesias and motor fluctuations, both in animals\(^41\) and in humans.\(^42\) Such infusion therapies are, however, impractical for a number of reasons, for patients, caregivers and physicians alike. Hence, administration of COMT inhibitor with levodopa and a peripheral dopa-decarboxylase inhibitor 4 to 5 times a day is advocated.\(^43\) A newly launched 3-in-1 combination product called stalevo has the main benefits of being smaller in size and reducing the number of pills to be taken by the PD patient. Pharmacokinetic studies have demonstrated bioequivalence between stalevo and corresponding dosages of entacapone plus levodopa/carbidopa.\(^44\)

**Starting Therapy: When, How and Why?**

Obviously, then, the long-term outcome for patients with PD depends on the selection, timing, dose, and order of medication administration at an early stage. Early treatment of PD comprises non-pharmacologic treatment and the consideration of initiation of neuroprotective therapy and symptomatic treatment.\(^45\)

**Non-pharmacologic Interventions**

Non-pharmacologic interventions are imperative in the good management of PD patients – these include patient and caregiver education, support services including PD support groups and rehabilitation services, and exercise. Exercise has been shown in rodent models of PD to induce behavioural recovery and to diminish the neurochemical deficits.\(^46\) This is possibly due to enhanced dopamine synthesis through a calmodulin-dependent system,\(^47\) or possibly through the formation of anti-inflammatory signal molecules such as interleukin-10 and adrenocorticotropin.\(^48\) Consistent with these findings is the finding that PD patients feel more fatigue when they are more sedentary and have poorer functional capacity and physical function.\(^49\) Nutritional advice is often helpful, and patients need to be educated on the possibility of dietary amino acids competing with levodopa for absorption from the gastrointestinal tract, and for transport into the brain, potentially causing erratic and unpredictable responses to levodopa therapy.\(^50\) It is prudent to advise patients to refrain from a protein meal 45 minutes before and a half hour after taking their levodopa.\(^45\)

**Neuroprotective Strategies**

Ideally, patients should be given neuroprotective therapy to slow, stop or reverse the neurodegenerative process. The insights gleaned in recent years to the aetiopathogenesis of the disease offer hope that these strategies are within the horizon. In the DATATOP study, deprenyl (selegiline)
Symptomatic Treatment

confirmed in large-scale trials. Interestingly, DAs have coenzyme Q10 have shown benefit, but this needs to be transported chain, has been trialled in PD because of the mitochondrial dysfunction that has been demonstrated to be present in PD. Small-scale studies using high-dose coenzyme Q10 have shown benefit, but this needs to be confirmed in large-scale trials. Interestingly, DAs have emerged as neuroprotective candidates, based on laboratory studies demonstrating their ability to protect dopaminergic and non-dopaminergic neurons in both in vitro and in vivo models. Other potential neuroprotective agents are being investigated, but the difficulty in defining an outcome variable for measuring disease progression poses an obstacle to assessing these agents. Time to reach a clinical milestone such as the need for levodopa therapy, comparison of baseline motor scores with those of drug treatment after a drug washout period and more recently, studies employing surrogate neuroimaging markers, such as FD-PET (fluoridopa positron emission tomography) and β-CIT-SPECT (iometophane single-photon emission computed tomography), have allowed workers in the field to make some headway.

Symptomatic Treatment

Symptomatic treatment is considered for the PD patient with the development of functional disability, which varies with the individual. The goal of therapy is, of course, to use the least amount of medication that reverses the disability. Levodopa is the most effective antiparkinsonian agent, but DAs are preferred as first-line agents for several reasons. In line with the belief that pulsatile stimulation of dopaminergic receptors predisposes patients to the development of dyskinesias, DAs in clinical use have longer half-lives than levodopa, and may have a longer duration of symptomatic effect. Levodopa has been shown to be neurotoxic in in vitro experiments, although neurotoxicity has not been shown in vivo. Rascol et al studied the incidence of dyskinesias in patients with early PD who were given ropinirole or levodopa to determine which should be given as initial therapy. The primary outcome measure was the development of dyskinesias. Thirty-four per cent of the patients in the ropinirole group were able to complete the 5-year study without requiring levodopa supplementation. The patients receiving ropinirole were also less liable to develop dyskinesias than those receiving levodopa. Other studies have since demonstrated that PD can be successfully treated with DA alone for up to several years.

Use of DAs, however, is not free of problems. In 1999, Frucht reported sudden irresistible sleep attacks in patients taking ropinirole and pramipexole, which ceased when the patients stopped taking the medications. Razmy et al assessed excessive daytime sleepiness in patients taking ergot and non-ergot DAs, and found that the total dopaminergic dose rather than the specific DA used caused daytime sleepiness. Cognitive impairment, including hallucinations, psychosis and confusion, are more prone to occur in the elderly. Pulmonary and retroperitoneal fibrosis, erythromelalgia and Raynaud’s-like phenomena have been described in association with the ergot-derived DAs, and are thought to be less common in the non-ergot DAs. Fibrotic pericardial and valvular heart disease have recently been reported with ergot-derived DAs. Pramipexole has been reported to be associated with peripheral oedema, but to date the non-ergot DAs have been free of the fibrosis associated with the ergot-derived DAs.

Age is thus an important consideration when initiating antiparkinsonian therapy. In young patients, because of the longer treatment horizon, it is preferable to initiate therapy with a non-ergot DA such as pramipexole or ropinirole. Older patients (usually taken as more than 70 years old) are usually commenced on levodopa therapy, because they have a shorter treatment horizon, are more liable to develop cognitive and psychiatric complications, and because they are thought to be less likely to develop motor fluctuations and dyskinesias with levodopa. Of course, it is mandated that the patient be cognitively intact before deciding to initiate therapy with a DA. It is not inconceivable that a hale and hearty 70-year-old with good cognitive function receives a DA, just as a 60-year-old who has mild dementia might be started on levodopa, rather than a DA.

Managing Other Motor Complications

In patients with poor initial response or who respond initially to medications, after which they fail to benefit, the diagnosis of atypical parkinsonism must be considered. Of course, some patients may require high doses of levodopa (up to 1000 to 1500 mg/day) before they show demonstrable benefit. Strategies to treat subtherapeutic response to dopaminergic agents includes combination therapy (adding levodopa or dopamine agonist as well as COMT inhibitors) and possibly the use of controlled-release formulations.

A variety of treatment strategies have been tried, in an effort to reduce dyskinesias, which can be very disabling for the patient. Agents which offer promise include NMDA antagonists such as Amantadine, nootropics such as levetiracetam, and sedatives such as zolpidem. Recently, the potential role of novel agents such as adenosine A2A antagonists in the amelioration of dyskinesias has
been raised.70

Surgical treatment of Parkinson’s disease has offered new hope to sufferers of the disease, and to their treating physicians. It has come a long way since the last century, when lesions of the corticospinal tract were noted to improve the symptoms of PD. In the 1950s, Cooper71 accidentally ligated the anterior choroidal artery, causing a thalamic infarct and serendipitously bringing about improvement in the tremor of PD. Surgical therapies were largely abandoned in the 1960s with the advent of levodopa therapy. Surgical treatment has made a comeback in recent years, with deep brain stimulation, developed by Benabid et al.72 Targets now include the subthalamic nucleus, globus pallidus and thalamus.

Much hype has surrounded the possibility of regeneration of dopaminergic neurons by means of fetal cell transplantation.73 Lindvall et al74 successfully transplanted fetal ventral mesencephalic neurons into the striata of patients with PD, who improved clinically. Unfortunately, in 2 recent randomised double-blind studies in which patients either received fetal transplants or had sham surgery, the results were less impressive, young patients experiencing clinical benefit but not older patients (despite graft survival) in the study by Freed and Fahn,75 and similar results in Olanow’s study.76 In both studies, patients developed off-medication dyskinesias.

Conclusions

Treatment aims in PD include the provision of symptomatic relief, reduction of functional disability, halting or slowing of the neurodegenerative process and the prevention of long-term complications by proper initiation of therapy. Neuroprotective strategies are currently being developed, but evidence that MAO inhibitors such as selegiline provide neuroprotection have prompted movement disorders specialists to commence therapy with this drug. In view of the overwhelming evidence supporting the delay of dyskinesias and lately the possible neuroprotective role of dopamine agonists, therapy should be initiated with a (preferably non-ergot) dopamine agonist in the younger patient. For the elderly patient over the age of 70 (and some would advocate in those over 65), in view of the potential deleterious effects on sedation, it is preferable to initiate therapy with levodopa (in combination with a peripheral dopa-decarboxylase). Dopagonist monotherapy is only effective for a few years, and add-on therapy with levodopa is often warranted. Finally, the addition of a COMT inhibitor to levodopa may help to increase the availability of levodopa centrally, ensure a smooth profile of dopaminergic stimulation and thus delay the development of motor complications.

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March 2005, Vol. 34 No. 2
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