New Concepts in the Management of Parkinson's Disease

a report by
Fabrizio Stocchi

Scientific Institutes for Research, Hospitalisation and Healthcare, San Raffaele, Rome
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Parkinson's disease (PD) is a disorder of unknown cause affecting 1% of people over 60 years of age, making it the second most common neurodegenerative disorder after Alzheimer's disease in this population. The motor symptoms associated with PD are thought to arise from dopamine deficiency, although the pathophysiology of various Parkinsonian symptoms is not yet fully understood. Many axial motor symptoms – e.g. gait problems, postural instability – and non-motor symptoms – e.g. dysarthria, dysphagia, pain, diplopia and urinary urgency – do not respond to dopamine replacement and are thought to be due to degeneration of non-dopaminergic neurons.

As a dopamine replacement therapy, levodopa has become and remains the standard of care for patients with PD. While levodopa clearly improves motor symptoms, allowing many patients to better perform daily activities and continue working, a major disadvantage of long-term standard levodopa therapy is the development of disabling motor complications characterised by 'wearing off', dyskinesias and 'on–off', which occur in up to 80% of patients and can be even more disabling than the disease itself. Levodopa was introduced in the therapy of PD in 1968 and other drugs were introduced later, but questions remain: when should dopaminergic treatment be started, how should levodopa be administered when first introduced and is there a way to minimise motor complications?

When to Start Treatment

There is no evidence indicating when dopaminergic treatment should be started in PD patients. However, until now the recommendation that drug treatment should be delayed until the symptoms of PD significantly limit the patient's motor functions has become established teaching and is included in many guidelines. The rationale for this is to protect the patients from unnecessary side effects, particularly the motor complications associated with levodopa. Moreover, a view also developed that patients in whom the introduction of pharmacological treatment is delayed would respond for longer when the drugs were introduced. Despite the lack of evidence supporting this theory, it is followed by the majority of clinicians.

Fabrizio Stocchi is a Professor of Neurology, Consultant in Neurology and Director of the Parkinson's Disease and Movement Disorders Research Centre at the Scientific Institutes for Research, Hospitalisation and Healthcare, San Raffaele, Rome. Also, he is a Scientific Advisor at the Institute for Parkinson's Disease Research in Vicenza. His research activities have centred on neuropharmacology in the field of movement disorders and neurodegenerative diseases. He has published many books and papers on Parkinson's disease, as well as conducting pre-clinical research into the disease. Professor Stocchi received his MD from the University of L'Aquila and his PhD from the University of Catania.

E: fabrizio.stocchi@sanraffaele.it

The clinical onset of PD is directly associated with a series of functional changes in basal ganglia circuits and their target projections. Bearing in mind that denervation in PD begins approximately six years before the appearance of symptoms, basal ganglia have a remarkable capacity to cope with progressively lower levels of dopamine-activating compensatory mechanisms. The appearance of symptoms indicates the point of failure to adequately deal with dopamine depletion.

Recently, Schapira and Obeso proposed that early restoration of basal ganglia physiology could support compensatory events and delay the irreversible modification of circuitry that characterises the clinical progression of PD. This idea makes sense and may explain the results of the elledopa study and the rasagiline delayed start trial. In fact, in the elledopa study the patients treated with placebo showed a significant difference in disease severity compared with the patients treated with levodopa, even after two weeks of therapy washout. It may be argued that two weeks is not long enough to rule out the long duration response of levodopa and that rasagiline may have a neuroprotective effect. However, the theory that there is a connection between the early compensatory effect of a symptomatic drug and better long-term symptom control is fascinating. Moreover, some deformity of the hands or spine may be avoided by early therapy.

Levodopa Dosing

The appropriate dosage of levodopa was arbitrarily decided when it was introduced into PD treatment. In fact, the dosage of levodopa was not established on the basis of its pharmacokinetic proprieties or on the basis of a dose-finding study, but solely on the observation that three daily doses were able to restore mobility and control symptoms in the majority of patients. In the last 35 years, much research has focused on motor complications, but not much thought has been given to the impact of the way we administer levodopa in the early stage of the disease. There are a number of studies reporting the incidence of motor complications, and the elledopa study showed that after just nine months of treatment with levodopa 200mg three times a day, 20% of patients experienced wearing off and 16% had dyskinesias. However, the classic way to administer levodopa has never been changed. Animal data indicate that dyskinesias are less severe when levodopa is administered more frequently during the day, in combination with a catechol-o-methyltransferase inhibitor. It is time to reconsider the way levodopa is administered.

The Concept of Continuous Dopaminergic Stimulation and Motor Complications

It has now been established that substantia nigra pars compacta dopamine neurons fire tonically at a rate of 3–6Hz, independent of movement, with

increased firing activity or bursting occurring primarily in response to events such as reward or novel stimuli. Furthermore, microdialysis and amperometry show that striatal dopamine levels are relatively constant. As dopamine re-uptake by dopamine nerve terminals is robust and finely regulated, it is highly likely that synaptic dopamine levels and activation of striatal dopamine receptors are also relatively constant.

The situation changes in the dopamine-denervated state. Here, the loss of nigral neurons impairs dopaminergic modulation of striatal medium spiny neurons, leading to increased cortico-striatal activity, and plastic changes in the striatum manifest themselves as long-term depression and an impaired capacity to form long-term potentiation. Furthermore, dendritic spines of striatal neurons – which are the sites of glutamate–dopamine interactions – are reduced in density and size in the denervated striatum of both animal models and PD patients. As a consequence of these and other changes, there is a loss of somatotopic selectivity of neuronal firing and reduced inhibitory centre surround in response to peripheral stimuli in both the striatum and globus pallidum intern. These changes fundamentally impair the capacity of the basal ganglia to appropriately select and facilitate normal movement.

Standard doses of levodopa/carbidopa do not restore basal ganglia physiology to normal. The exogenous administration of intermittent doses of a short-acting formulation of levodopa (half-life of about 90 minutes) results in large and uncontrolled oscillations in striatal dopamine levels, which increase with disease progression and the progressive loss of the capacity of striatal dopamine terminals to buffer fluctuations in plasma levodopa levels. This changes the normal situation, in which striatal dopamine receptors are continuously exposed to dopamine, to one in which they are exposed to pathologically high and low concentrations of dopamine. This discontinuous activation of dopamine receptors is referred to as pulsatile stimulation, and further destabilises an already abnormal basal ganglia network. We and others have demonstrated that continuous intra-intestinal infusion of levodopa induces a significant reduction in both 'off' time and dyskinesia in comparison with intermittent doses of a standard oral formulation of the drug. As part of this study, plasma levodopa pharmacokinetics were analysed. This study suggests that continuous levodopa infusion prevents motor complications and this may be due to the continuous stimulation induced by constant levodopa levels, which avoids the low plasma levodopa-trough levels seen with oral administration of the drug.

Over the past decade, substantial evidence has accumulated indicating that levodopa-related motor complications in PD are associated with pulsatile or discontinuous stimulation of striatal dopamine receptors, and may be reversed or prevented by long-acting dopaminergic therapies that theoretically provide more continuous stimulation of striatal dopamine receptors. The future management of PD should take into account these new ideas and, with the help of new drugs, the quality of life of PD patients can be improved. ■

Parkinson's Disease – Events for the Diary

2008

23–26 August
12th European Federation of Neurological Societies
Madrid, Spain
www.kenes.com

28–29 August
LSVT LOUD Workshops – Voice Treatment for Adults and Children with Neurological Disorders, with a Speciality in Parkinson's Disease
Helsinki, Finland
www.gleecoinc.com

10–13 September
10th International Conference on Neural Transplantation and Repair
Freiburg, Germany
www.asntr.org/events

4–5 October
7th Euroyapmeet Conference – European Parkinson's Disease Association
Zagreb, Croatia
www.epda.eu.com/euroYap/2008

16–19 October
6th International Congress on Mental Dysfunctions and Other Non-motor Features in Parkinson's Disease and Related Disorders
Dresden, Germany
www.kenes.com/pdment2008

13–14 November
LSVT LOUD Workshops – Voice Treatment for Adults and Children with Neurological Disorders, with a Speciality in Parkinson's Disease
Sheffield, England
www.gleecoinc.com

2009

15–17 February
5th Annual Update Symposium on Clinical Neurology and Neurophysiology
Tel Aviv, Israel
www.neurophysiology-symposium.com

7–11 June
The Movement Disorder Society 13th International Congress of Parkinson's Disease and Movement Disorders
Paris, France
www.movementdisorders.org/congress

15–17 October
41st International Danube Symposium for Neurological Societies and Continuing Education
Linz, Austria
www.szote.u-szeged.hu/neur/danube/nl13.htm

13–16 December
XVIII WFN World Congress on Parkinson's Disease and Other Movement Disorders
Miami Beach, FL, US
www2.kenes.com/Parkinson

15–17 February
5th Annual Update Symposium on Clinical Neurology and Neurophysiology
Tel Aviv, Israel
www.neurophysiology-symposium.com