Scientific Rationale for Continuous Dopaminergic Stimulation in Parkinson’s Disease

a report by

M Maral Mouradian

William Dow Lovett Professor of Neurology and Director, Centre for Neurodegenerative and Neuroimmunologic Diseases, Robert Wood Johnson Medical School
University of Medicine and Dentistry of New Jersey
DOI:10.17925/ENR.2006.00.02.62

M Maral Mouradian is the William Dow Lovett Professor of Neurology and Director of the Center for Neurodegenerative and Neuroimmunologic Diseases in the Department of Neurology, Robert Wood Johnson Medical School, New Jersey, US. She also holds joint professorships in the Department of Neuroscience and Cell Biology and in the Department of Molecular Biology, Microbiology and Immunology at the same institution.

During the last 13 years of her National Institutes of Health (NIH) tenure, Dr Mouradian directed the Genetic Pharmacology Unit of the National Institute of Neurological Disorders and Stroke (NINDS)/NIH prior to assuming her current posts at the University of Medicine and Dentistry of New Jersey. In addition to carrying out basic and translational research, she evaluates and treats patients with Parkinson’s disease (PD) and conducts clinical research. A member of the Scientific Advisory Board of the American Parkinson Disease Association and the editorial board of Neurology, she is an associate editor of Pharmacology and Therapeutics. She is the recipient of the NIH Award of Merit and a member of the Alpha Omega Alpha honour medical society. After obtaining her medical education and neurology training, Dr Mouradian joined the NIH in Bethesda, Maryland, US, where she obtained further training in clinical research on PD, as well as in molecular biology.

Since its introduction nearly four decades ago, levodopa (L-dopa) continues to be the most efficacious agent in ameliorating many of the motor symptoms of Parkinson’s disease (PD). This dopamine precursor improves quality of life, reduces disability and prolongs independent living and life expectancy.

A good response to L-dopa is often used to help make the diagnosis of clinical PD and is used as a benchmark against which other newer anti-parkinsonian agents are evaluated. The initial stable response to infrequent oral dosing with L-dopa is gradually replaced by shorter responses known as ‘wearing-off phenomenon’, necessitating more frequent dosing as well as the addition of agents that slow down the catabolism of the active derivative dopamine, such as inhibitors of catechol-O-methyl transferase and monoamine oxidase. Eventually, the shortened and unstable motor response becomes unpredictable with no apparent relation to the timing of L-dopa intake. This is known as the ‘on-off’ phenomenon.

The clinical syndrome is complicated further with the emergence of involuntary movements that are often choreiform, but sometimes dystonic in nature. The significance of these motor response complications lies in the fact that they affect the majority of patients with PD treated chronically with L-dopa, represent a major source of disability in many patients ridding that caused by the underlying disease itself, and are the commonest reason for surgical intervention in PD.

Causess for the Unstable Motor Response to L-dopa

Both peripheral pharmacokinetic factors and central pharmacodynamic changes contribute to the unstable response to L-dopa. The short plasma half-life of L-dopa of around 90 minutes is a clear limitation, necessitating frequent dosing in advanced cases in order to maintain therapeutic blood and brain levels. Absorption of L-dopa takes place primarily in the duodenum and is influenced by erratic gastric emptying and food boluses.

Competition with dietary large neutral amino acids for entry across the blood-brain barrier can interfere with the access of L-dopa to its site of action.

While these peripheral pharmacokinetic factors are no different in the early versus the advanced disease, they assume clinical relevance only in advanced patients because of the fundamental central changes that occur in the brain in late stages of the disease. The fluctuating plasma L-dopa levels go unnoticed in early disease because of the wide therapeutic window for this drug between its therapeutic anti-parkinsonian effect and the ‘toxic’ dyskinesias.

As the disease progresses, the therapeutic window narrows significantly, allowing the fluctuations to become clinically apparent. When circulating L-dopa levels fall below a certain threshold, parkinsonian symptoms re-emerge, but when the drug levels exceed the upper limit of the therapeutic window, dyskinesias dominate.

Only during the brief periods when the drug levels are within the narrow therapeutic window are patients mobile with no dyskinesias. Besides the narrowing of the therapeutic window, the dose response curve for the motor effects of L-dopa within the therapeutic dose range changes from a relatively linear curve with a small slope in early disease to an S-shaped curve encompassing a virtually vertical slope. Small oscillations in plasma L-dopa levels are translated to marked changes in the clinical response, sending the patient to abrupt and unpredictable shifts between bradykinetic ‘off’ states and dyskinetic ‘on’ states.

One of the central prerequisites for the unstable motor response to L-dopa is severe nigrostriatal denervation in advanced disease. Clinical experience has shown that L-dopa given to non-parkinsonian patients produces no dyskinesias in the absence of nigral neuronal degeneration. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys with upwards of 95% loss of dopamine neurons develop dyskinesias within days of starting L-dopa therapy, whereas partially lesioned animals...
WORLD PARKINSON'S DISEASE DAY

Promoting a constructive dialogue between science and society

euroYAPmeet conference
for younger people with Parkinson's disease

EPDAPlus

EPDA
EUROPEAN PARKINSON'S DISEASE ASSOCIATION

www.epda.eu.com

Rewrite Tomorrow

EPNN JOURNAL

MULTIDISCIPLINARY CONFERENCE

* PARKINSON'S DISEASE * COPING STRATEGIES

tel/fax: +44 (0)1732 457 683

email: info@epda.eu.com
are much more resistant to the development of L-dopa-induced dyskinesias.

With advancing PD, as the number of dopamine-producing nigral neurons decrease from about 50% at the onset of symptoms down to about 20% or less, striatal dopaminceptive medium spiny neurons become increasingly exposed to the fluctuations in plasma and brain levels of L-dopa and, hence, dopamine. The presence of a normal complement of nigral dopaminergic neurons in non-parkinsonian individuals shields the striatum from oscillating L-dopa levels.

Additionally, individuals who have developed severe subacute Parkinsonism, as a result of accidental exposure to the dopaminergic neurotoxin MPTP, have massive nigrostriatal degeneration and manifest L-dopa-induced motor response fluctuations and dyskinesias within months of starting therapy. Patients with PD due to mutations in the parkin gene and severe neuronal loss also develop dyskinesias early on.

Finally, several prospective, double-blind, controlled studies have compared the time to onset of motor response complications in untreated patients randomised to initiate therapy with either standard oral L-dopa or relatively longer-acting dopamine agonists. While dopamine agonist therapy per se is associated with less dyskinesias, those who start with a dopamine agonist first and then switch to L-dopa develop fluctuations at about the same time as those who start L-dopa from the outset. The latter finding suggests that the duration of disease, and by implication the degree of neuronal loss, is an important element in the genesis of motor complications.

Experimental observations suggest that the second prerequisite for the development of motor fluctuations in PD is long-term intermittent L-dopa administration. In monkeys rendered parkinsonian by MPTP, repeated dosing with oral L-dopa produces dyskinetic movements, while treatment with a long-acting dopamine agonist is associated with considerably less or no dyskinesias.

While such an observation may be attributed simply to the lesser tendency of dopamine agonists than L-dopa to induce dyskinesias, studies comparing the same dopaminomimetic agent given in different treatment schedules have yielded similar results. Parkinsonian monkeys develop involuntary movements if apomorphine is injected daily, but not if the same drug is delivered at the same dose level through an implant releasing apomorphine continuously. Similarly, 6-hydroxydopamine-lesioned rats injected twice daily with L-dopa rotate much more that those in which L-dopa is infused continuously through a pump. Over time, such intermittently treated mice develop the clinical equivalent of ‘wearing-off’ phenomenon with reduced duration of motor effects of L-dopa, a phenomenon that is dependent on the severity of dopamine neurons loss.

**Pathophysiological Changes with Advancing PD and Intermittent L-dopa Therapy**

Support for the notion that continuous dopaminergic stimulation is superior to intermittent therapy stems from the fact that, under normal conditions, dopamine neurons in the substantia nigra pars compacta fire tonically at a steady slow rate of about four hertz, regardless of whether the animal is at rest or moving. Striatal dopamine concentrations are stable as well. With the anticipation of reward or novel stimuli, dopamine neurons can fire in bursts, but the efficient re-uptake by dopamine transporters allows the maintenance of intrasynaptic dopamine concentrations to be fairly steady. In early PD, when half the dopaminergic neurons are still intact, dopamine can be synthesised and stored in slowly turning over vesicles, only to be released tonically, thus shielding the post-synaptic dopamine receptors from oscillations in circulating L-dopa levels.

With advancing disease, as more and more neurons disappear and the capacity to store dopamine and release it tonically is diminished, standard intermittent oral therapy with anti-parkinsonian agents with a relatively short half-life, such as L-dopa, result in oscillations in striatal intrasynaptic dopamine levels that mirror the oscillations in plasma. A neurotransmitter system that is designed to function normally tonically is replaced with an artificially pulsatile system. This non-physiologic situation is believed to underlie the altered pharmacodynamics of the L-dopa response.

Biochemical and molecular aberrations have been documented in experimental models as a result of intermittent stimulation of the nigrostriatal dopaminergic system.

Repeated administration of short-acting dopaminomimetics in rodent and non-human primate models of PD associated with dyskinesias result in altered expression of various peptide transmitters and signalling molecules, including enkephalin, dynorphin, neurotensin, Fos and JunB proteins, ERK1/DAR.P32 and D1 signalling molecules. Some of these changes have also been detected in post-mortem brain tissue of PD patients.
including substantially elevated preproenkephalin in patients who had L-dopa-induced dyskinesias compared to patients treated with L-dopa but did not manifest dyskinesias or to normal control individuals. In MPTP monkeys treated with a D2 dopamine agonist, neither the enkephalin changes nor dyskinesias seen with intermittent therapy occur if the drug is given continuously.

Dopamine receptor-mediated mechanisms modulate the sensitivity of ionotropic glutamatergic receptors of the N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) types on striatal medium spiny neurons. With dopaminergic denervation, and to a greater extent with intermittent dopaminergic therapy, the sensitivity of these glutamate receptors is increased. Changes in the phosphorylation state of certain sub-units of these glutamate receptors enhance cortical excitatory input to these spiny efferent neurons, thus altering striatal output in ways that compromise motor function. These transmitter modifications reflect increases in the firing rates and other burst parameters of medium spiny neurons that appear to underlie changes in motor behaviour.

Advantages of Continuous Dopaminergic Stimulation

The merits of continuous dopaminergic stimulation have been amply demonstrated in stabilising the motor fluctuation in patients with advanced PD. This has been shown both with L-dopa and dopamine agonists. L-dopa infused continuously intravenously or intraduodenally markedly reduces oscillations in plasma drug levels and ‘wearing-off’ fluctuations and dyskinesias. Dopamine agonists have similar properties when delivered continuously, such as lisuride and apomorphine infused subcutaneously, or rotigotine transdermally.

While the question whether continuous anti-parkinsonian therapy postpones or minimises future genesis of fluctuations and dyskinesias has been convincingly demonstrated in primate and rodent models as described above, proving the same notion in the clinical setting has been more challenging. In a prospective study, L-dopa-treated Parkinson patients experiencing severe ‘off’ times and dyskinesias were randomised to either continue receiving intermittent oral L-dopa or to switch to a continuous subcutaneous infusion of lisuride. As expected, the lisuride infusion group showed marked improvement in ‘off’ times and dyskinesias compared with the oral L-dopa group. After a period of four years, ‘off’ time had improved by around 71% in the infusion group and worsened by 21% in the oral L-dopa group. Dyskinesias were reduced by 49% in patients infused with lisuride, but increased by 59% in patients given oral L-dopa. These encouraging observations support the notion that long-term continuous dopaminergic stimulation minimises motor response complications.

The plasticity of the basal ganglia circuitry that underlie the central pharmacodynamic changes associated with long-term intermittent dopaminergic stimulation also appears to be reversible, at least to some extent. Motor fluctuations of the unpredictable ‘on-off’ type, which tend to be quite resistant initially even to continuous dopaminomimetic therapy, are eventually ameliorated with persistent drug delivery such as with intravenous infusion of L-dopa. Abruptly switching back to intermittent therapy does not revert the patients to their baseline severity of motor fluctuations. Rather, a relatively smooth motor response is enjoyed for at least several more days until the beneficial effect of continuous therapy eventually dissipates. The latter observation suggests that continuous therapy had produced plastic changes in the basal ganglia, which lasted well beyond the removal of the physiologic stimulation and re-introduction of intermittent therapy. The advantages of continuous dopaminergic therapy in PD can be gained in both early and advanced disease where fluctuations can be ameliorated both by stabilising circulating drug levels and by normalising some of the central pharmacodynamic alterations attending chronic, non-physiologic, intermittent stimulation.

A version of this article containing full references can be found in the Reference Section on the website supporting this briefing (www.touchneurology.com).
References

Duodopa contains 1 ml contains 20 mg levodopa and 5 mg carbidopa monohydrate. 100 ml contain 2000 mg levodopa and 500 mg carbidopa. Pharmaceutical form: intestinal gel. Therapeutic indications: Treatment of advanced levodopa-resistant Parkinson’s disease with severe motor fluctuations and hyper-dyskinesias when available combination of Parkinson’s medicinal products have not given satisfactory results. Posology and method of administration: For long-term administration, the gel should be administered with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy with an outer transabdominal tube and an inner intestinal tube. Alternatively, a radiological gastrostomy may be considered if percutaneous endoscopic gastrostomy is not suitable for any reason. Establishment of the transabdominal port and dose adjustments should be carried out in association with a neurologist or a radiologist. A temporary nasoduodenal tube is recommended to find out if the patient responds favourably to this method of treatment and to adjust the dose before treatment with a permanent tube is started. The dose should be adjusted to an optimal clinical response for the individual patient, which may require several days. Carbidopa is not normally prescribed. The usual starting dose of Duodopa® is 5-10 ml corresponding to 100-200 mg levodopa. The total morning dose should not exceed 15 ml (300 mg levodopa). Continuous maintenance dose: The maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The dose should be calculated according to the patient’s previous daily intake of levodopa. When supplementary medicines are administered, the total dose of Levodopa should be adjusted. The continuous maintenance dose is adjusted individually and should be kept within a range of 1.0-1.5 ml/hour (200-300 mg/kg/day) and is usually 2.4 ml/hour (480-720 mg/kg/day). In exceptional cases, a higher dose may be needed. Extra bolus dose: To be given as required if the patient becomes hypokinetic during the day. The extra dose should be adjusted individually, normally 0.5-2.0 ml. In rare cases a higher dose may be needed. If the need for extra bolus doses exceeds 15 ml/day, the total dose maintenance dose should be increased. After the initial dose setting, fixed adjustments of the morning bolus dose, the maintenance dose and extra bolus doses should be carried out over a few weeks. If medically justified Duodopa® may be administered during the night. Monitoring of treatment: A sudden deterioration in treatment response with recurring motor fluctuations should lead to the suspicion that the distal part of the tube has become displaced from the duodenum into the stomach. The location of the tube should be determined by X-ray and the end of the tube repositioned to the duodenum under radiological control. Contraindications: Hypersensitivity to levodopa, carbidopa or any of the excipients; pancreatitis or diabetes; severe liver and renal insufficiency; severe heart failure; severe cardiac arrhythmia; acute stroke; non-selective MAO inhibitors and selective MAO type B inhibitors must not be given concomitantly, and should be withdrawn at least two weeks before initiation of Duodopa®, conditions in which adrenergic are contraindicated. Special warnings and precautions: for use: Duodopa® is not recommended for the treatment of drug-induced extrapyramidal reactions. Throes should be kept under control with careful observation of patients with Parkinson’s disease. As levodopa has an antiparkinsonian effect, in the absence of Parkinson’s disease. Patients with chronic wide-angle glaucoma may be treated with Duodopa® in combination with antihypertensive drugs. In cases in which adrenergic are contraindicated due to the central neurological activity of  dopamine. Patients should be carefully observed when the dose of levodopa/carbidopa combinations are abruptly reduced or discontinued, especially if the patient is receiving antidepressants. Due to the presence of levodopa, patients should be monitored for signs of dopamine induced dyskinesias. Parkinson’s disease and the use of Duodopa® should be reviewed in patients with documented adverse events related to levodopa. Caution is needed in patients w