

Research Review

Levodopa in the Treatment of Parkinson's Disease: Current Controversies

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Abstract: Levodopa is the most effective symptomatic agent in the treatment of Parkinson's disease (PD) and the "gold standard" against which new agents must be compared. However,

there remain two areas of controversy: (1) whether levodopa is toxic, and (2) whether levodopa directly causes motor complications. Levodopa is toxic to cultured dopamine neurons, and this may be a problem in PD where there is evidence of oxidative stress in the nigra. However, there is little firm evidence to suggest that levodopa is toxic in vivo or in PD. Clinical trials have not clarified this situation. Levodopa is also associated with motor complications. Increasing evidence suggests that they are related, at least in part, to the short half-life of the drug (and its potential to induce pulsatile stimulation of dopamine receptors) rather than to specific properties of the molecule. Treatment strategies that provide more continuous stimulation of dopamine receptors provide reduced motor com-

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Received 20 August 2003; Revised 3 May 2004; Accepted 5 May 2004

Published online 30 July 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20243

plications in MPTP monkeys and PD patients. These studies raise the possibility that more continuous and physiological delivery of levodopa might reduce the risk of motor complications. Clinical trials to test this hypothesis are underway. We

review current evidence relating to these areas of controversy. © 2004 Movement Disorder Society

Key words: Parkinson's disease; levodopa; neurotoxicity; dyskinesia; motor complications

Since its introduction more than 30 years ago, levodopa (L-dopa) therapy has revolutionized the treatment of Parkinson's disease (PD), providing marked symptomatic benefits to virtually all PD patients and increasing the time that PD patients can enjoy independent activities of daily living, employability, and possibly even life span. Although the drug is extremely effective, two main areas of controversy exist. The first relates to whether or not L-dopa is toxic to dopamine neurons. L-Dopa can generate cytotoxic reactive oxygen species (ROS) by way of the oxidative metabolism of dopamine or via autooxidation. This has led to theoretical concerns that L-dopa might be toxic to dopamine neurons, and might accelerate the rate of degeneration of nigral neurons in PD. Indeed, L-dopa can be toxic to cultured dopaminergic neurons; however, there is little or no evidence from in vivo models to suggest that L-dopa treatment damages nigral neurons in PD. Indeed, there is evidence suggesting that under some circumstances the drug might be protective and have trophic effects. A second area of controversy is when L-dopa treatment should be initiated. Although L-dopa is the most effective drug for the symptomatic treatment of PD, the high prevalence of motor complications (motor fluctuations and dyskinesias) associated with chronic L-dopa treatment is a troublesome limitation. This has led some physicians to advocate that the initiation of L-dopa treatment be delayed. Others, however, believe that the motor complications associated with L-dopa therapy are primarily the result of disease severity and the method of delivery, and recommend that L-dopa therapy should be introduced early in the course of the disease because of its striking symptomatic effects. This review will consider evidence bearing on these controversies.

L-DOPA AND NEUROTOXICITY

In Vitro Data

Numerous studies have demonstrated the potential of L-dopa (or dopamine) to exert toxic effects on cultured dopaminergic neurons.¹⁻³ Both L-dopa and dopamine are known to undergo autooxidation leading to the formation of highly reactive oxygen species (ROS), which include quinones, semiquinones, superoxide radical, hydrogen peroxide, and hydroxyl radical.⁴ These have the potential

to damage critical biomolecules such as DNA,^{5,6} proteins,⁷ and lipids,^{8,9} and ultimately to cause cell death. Exposure to high levels of dopamine and L-dopa reduces the number of tyrosine hydroxylase (TH)-positive neurons in fetal rat mesencephalic cultures and other dopaminergic cell lines,^{1,10-17} and induces apoptotic cell death with cell shrinkage, membrane blebbing, and DNA fragmentation.¹⁸⁻²¹

The potential of L-dopa to induce ROS is relevant in PD because of evidence that the substantia nigra pars compacta (SNc) is in a state of oxidative stress. Post-mortem analyses show increased levels of the pro-oxidant ferrous iron (Fe^{2+})²²⁻²⁴ decreased mitochondrial complex I,^{25,26} and a reduction in levels of the antioxidant reduced glutathione (GSH)^{27,28} in the PD nigra. Furthermore, there is evidence of oxidative damage to lipids^{29,30} DNA,³¹ and proteins.^{32,33} On the other hand, most studies showing L-dopa toxicity in tissue culture used concentrations greater than 50 $\mu\text{mol/L}$.^{1,12,14-16,34} By contrast, peak plasma concentrations in PD patients are in the range of 10 to 20 $\mu\text{mol/L}$ ³⁵⁻³⁷ and only about 12% of orally administered L-dopa reaches the cerebrospinal fluid (CSF).³⁶ In these concentrations, L-dopa is not toxic to cultured dopamine neurons. Furthermore, most studies used culture systems that are relatively lacking in glial cells, which contain high concentrations of antioxidants and trophic factors. When glial cells are included in the culture system, dopaminergic neurons are relatively protected from L-dopa toxicity.^{17,38,39} It is noteworthy that levels of the antioxidant ascorbic acid are virtually undetectable in mesencephalic cultures.⁴⁰ By contrast, the concentration of ascorbic acid in human CSF is relatively high ($\sim 130 \mu\text{mol/L}$),⁴¹ and even higher in the brains of normal and PD patients.²⁸ When included in culture media, ascorbic acid provides almost complete protection from L-dopa toxicity.^{12,14,18,34,40,42}

In contrast to the above, there is evidence that under certain study conditions L-dopa can protect cultured dopamine neurons. Studies using glia-conditioned media have shown that L-dopa can elicit a neurotrophic effect manifest by increased cell survival and enhanced neurite outgrowth.^{1,17,43,44} In addition, exposure to low concentrations of L-dopa can protect dopamine neurons from subsequent exposure to pro-oxidants that would otherwise be toxic.¹⁴ These neuroprotective properties are

associated with increased expression of GSH^{14,43} and other antiapoptotic molecules,¹⁷ which are thought to occur in response to a L-dopa-mediated low-level injury. In support of this concept, it is noted that neuroprotective effects associated with L-dopa can be reversed by ascorbate, which prevents its autooxidation.^{1,45} This suggests that both the protection and neurodegeneration associated with L-dopa result from autooxidation and generation of free radicals, with protection occurring as a result of a low-level injury with activation of intracellular protective mechanisms, whereas toxicity results from damage that is sufficiently severe that it overwhelms the cell's defensive capacities.^{14,45} These effects also occur with analogues of L-dopa that undergo autooxidation (e.g., dopamine, apomorphine, catechol, and hydroquinone), but not with analogues that do not undergo autooxidation (e.g. 3-O-methyl-DOPA, tyrosine, and 2,4-dihydroxyphenylalanine).¹⁴

In summary, L-dopa may be toxic or protective to cultured dopamine neurons depending on study conditions. The significance of these *in vitro* findings with respect to the effect of L-dopa in PD is not known, and it is not certain that any findings in tissue culture models are directly relevant to PD where ascorbate levels are relatively high and the presence of glia may provide trophic support for neurons.

In Vivo Animal Experiments

Several studies have examined the potential of L-dopa to induce toxicity in normal animals and humans, as well as in animal models of PD. No reduction in the number of dopaminergic neurons was observed in the SNc of normal rats or mice chronically treated with high doses of L-dopa for up to 18 months.^{46–48} Similarly, there was no evidence of L-dopa-induced neurodegeneration in normal primates^{49,50} or non-parkinsonian humans.^{51,52}

L-Dopa has also been tested in rats with 6-hydroxydopamine (6-OHDA)-induced lesions of the nigrostriatal tract. One study reported that chronic L-dopa treatment was associated with a small reduction in the number of dopaminergic neurons in the ventral tegmental area,⁵³ but this result could not be duplicated by the same authors in a subsequent trial.⁵⁴ Indeed, in the latter study, 12 weeks of chronic L-dopa therapy was associated with a significant recovery in the number of TH-positive neurons. L-Dopa also promoted recovery of dopamine neurons with increased striatal innervation in another study in 6-OHDA-treated rodents.⁴⁷

To represent better the situation in PD, where the SNc is in a state of oxidative stress, L-dopa was administered in combination with buthionine sulfoximine (BSO) to cultured dopamine neurons and rodent pups.⁴⁵ BSO re-

duces the levels of the antioxidant glutathione, thereby inducing a state of oxidative stress. *In vitro*, the combination of L-dopa and GSH depletion acted synergistically to reduce the number of surviving dopamine neurons, and this could be prevented completely by the addition of ascorbate. In rodent pups, however, L-dopa was not toxic to dopamine neurons even when GSH levels were depleted by as much as 90%, far exceeding the reduction found in PD. This may reflect the presence of ascorbate in relatively high levels in normal and PD brains.

Clinical Trials

Recent clinical trials in PD patients have tested the possibility that L-dopa might be toxic. Two trials each demonstrated an increased rate of decline of imaging biomarkers of nigrostriatal function in patients treated with L-dopa in comparison with dopamine agonists.^{55,56} As there was no placebo control, it was not possible to determine if the difference in the rate of deterioration between these agents was related to a toxic effect of L-dopa or a protective effect of the dopamine agonists. It is also possible that these results relate to pharmacologic differences in the capacity of the drugs to induce regulatory changes in components of the nigrostriatal system.⁵⁷ These studies thus do not provide conclusive information on whether or not L-dopa is toxic in PD.⁵⁸

The recently completed ELLDOPA study⁵⁹ compared the rate of disease progression in untreated PD patients randomly assigned to receive one of three doses of L-dopa or placebo. The primary endpoint was the change in Unified Parkinson's Disease Rating Scale (UPDRS) motor score between untreated baseline and a final visit carried out after 9 months of treatment with study drug and 2 weeks of washout.⁵⁹ In this study, there was less deterioration from baseline in UPDRS motor score in L-dopa-treated patients than in controls. This does not suggest toxicity and indeed, is consistent with a protective effect. It is possible, however, that the washout was inadequate and that L-dopa is associated with a long-duration symptomatic effect that persists even after 2 weeks of withdrawal. Further, on neuroimaging studies carried out as part of this study, L-dopa treatment was associated with a greater rate of decline than placebo in a biomarker of nigrostriatal function. This result suggests that the drug might have a toxic effect, although here too a confounding pharmacologic effect can not be excluded. The ELLDOPA study thus does not resolve the issue of whether or not L-dopa is toxic in PD.

In the final analysis, it remains unclear as to precisely whether or not L-dopa has a toxic effect on dopamine neurons in PD, but there is no clear evidence that the drug has an adverse effect on disease progression. Ac-

cordingly, most physicians prescribe L-dopa based solely on considerations of its clinical efficacy and adverse event profile in individual patients.⁶⁰ Further clinical and imaging studies to help clarify whether or not L-dopa is toxic in PD are warranted.

L-DOPA AND MOTOR COMPLICATIONS

The major limitation to the chronic use of L-dopa is the development of motor complications (motor fluctuations and dyskinesias). These occur in approximately 50 to 80% of PD patients who have received L-dopa for more than 5 to 10 years,^{61,62} and are more likely to occur in patients with young onset PD.^{63,64} Motor complications can represent a major source of disability, and in the extreme can result in patients cycling between *on* responses complicated by severe dyskinesias, and *off* responses with disabling parkinsonism. The precise cause of motor complications is not known, but increasing evidence suggests that they are related to abnormal pulsatile stimulation of dopamine receptors (see below).

Pulsatile Stimulation of Striatal Dopamine Receptors

Over the past decade, our understanding of the organization of the basal ganglia has advanced considerably. Initial models of the basal ganglia proposed that parkinsonism and L-dopa-induced dyskinesia were related to a respective increase or decrease in the firing rate of basal ganglia output neurons.^{65,66} This explanation, however, does not account for many of the metabolic and physiologic changes found in these conditions, or more importantly why pallidotomy is associated with amelioration and not induction of dyskinesia.⁶⁷ It is now appreciated that the entire firing pattern is important in conveying information from the basal ganglia to brainstem and cortical motor regions to facilitate the selection of correct motor movements and inhibit undesired motor movements.⁶⁸⁻⁷¹

It is now known that normally nigrostriatal dopaminergic neurons fire continuously, independent of voluntary movement.^{72,73} Burst firing with increased dopamine release may occur in response to glutamatergic drive, reward, or anticipation of reward,⁷⁴⁻⁷⁷ but microdialysis studies do not report any significant increase in extracellular dopamine,⁷⁸ probably reflecting the highly efficient reuptake capacity of presynaptic terminals. Thus, in the normal brain, striatal dopamine levels, and activation of dopamine receptors on medium spiny striatal neurons remain relatively constant.

In contrast, in the dopamine-denervated state, striatal medium spiny neurons are deprived of the modulating effects of dopamine leading to the development of par-

kinsonian symptoms and the need for dopaminergic replacement therapy. With disease progression, striatal dopamine levels become increasingly dependent on the peripheral availability of exogenously administered L-dopa and there is a loss of the buffering capacity of remaining nigrostriatal terminals that regulate the uptake and release of dopamine. Fluctuations in plasma levels of a short-acting agent like L-dopa may thus be translated into fluctuations in striatal dopamine concentrations causing striatal dopamine receptors to be exposed to alternating high and low concentrations of dopamine. This pulsatile stimulation of denervated striatal dopamine receptors may force an already abnormal basal ganglia network to adapt to an even more abnormal situation. Indeed, pulsatile stimulation of denervated dopamine receptors has been shown to induce a variety of gene changes in striatal nerve cells and alterations in the electrophysiological firing pattern of basal ganglia output neurons.⁷⁹⁻⁸⁵

Dopamine denervation causes upregulation of preproenkephalin (PPE) mRNA and downregulation of dynorphin and substance P mRNA in both rodent and primate models of PD.⁷⁹⁻⁸² In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates, intermittent, pulsatile treatment with L-dopa induces dyskinesia within a few weeks.^{83,84} In these animals, L-dopa normalizes substance P gene expression but has no significant effect on, and may even upregulate PPE expression.^{81,85} By contrast, treatment with long-acting dopamine agonists normalize PPE and are not associated with dyskinesia in drug-naïve animals.^{86,87} Other gene changes associated with pulsatile stimulation and the development of dyskinesia include alterations in the Fos family of genes and prodynorphin, particularly in the rodent model.⁸⁸ Gene changes associated with dyskinesia are translated through as yet unknown mechanisms into neurophysiologic changes that include a decrease in the firing frequency of internal Globus Pallidus (GPi) neurons (as predicted by the classic model), as well as changes in the number and duration of pauses, bursts, and degree of synchrony.⁸⁹⁻⁹⁵ It is likely that it is the disruption of these abnormal firing patterns that accounts for the antidyskinetic effects of pallidotomy and deep brain stimulation.⁹⁶⁻⁹⁸

Factors Contributing to Pulsatile Stimulation

Two factors are thought to contribute to the development of pulsatile stimulation; disease severity and the half-life of the dopaminergic agent employed. With advancing disease, there are fewer remaining striatal dopamine terminals and consequently a reduced capacity to buffer fluctuations in striatal levels of L-dopa/dopamine.

This concept is supported by the rapidity with which motor complications develop with severe nigrostriatal degeneration compared with the longer latency before dyskinesias occur when there is milder disease. For example, motor complications develop within days after initiation of L-dopa in MPTP treated primates where there is approximately 90 to 95% cell loss^{83,84,99} and within weeks to months in patients with advanced PD¹⁰⁰ or MPTP-induced parkinsonism.^{101,102} In contrast, L-dopa induced dyskinesias tend to develop over years in patients with typical PD where nigrostriatal degeneration is not as advanced (40 to 60% cell loss)¹⁰³ and gradually become more severe over time.¹⁰⁴ In addition, levodopa does not cause dyskinesia in normal individuals.^{51,52}

The half-life of the dopaminergic agent employed also contributes to the likelihood of inducing pulsatile stimulation. In MPTP-treated primates, short-acting agents such as L-dopa,^{84,99} or D1 or D2 agonists such as quinpirole,¹⁰⁵ (+)-PHNO,¹⁰⁶ and SKF-82958¹⁰⁷ are more likely to induce motor complications than are long-acting dopamine agonists such as bromocriptine^{99,108} and ropinirole.^{108,109} These results were obtained even though dosages were titrated to ensure that animals were matched for behavioral response.^{108,109} Indeed, dyskinesias were observed when the short-acting dopamine agonist U-91356A was administered intermittently, but not when the same agent was administered continuously by infusion pump.¹¹⁰ In this study, gene changes associated with dyskinesia were seen with the intermittent administration of the drug but not when the drug was delivered continuously.¹¹¹ These studies illustrate that motor complications relate to the manner in which a dopaminergic agent is administered and its potential to induce pulsatile stimulation. They suggest further that the risk of motor complications in PD might be reduced by initiating treatment with a long-acting dopaminergic agent that avoids pulsatile stimulation of striatal dopamine receptors.

Clinical Trials

Several prospective, randomized, double-blind, controlled trials have been carried out in PD patients comparing initial therapy with L-dopa to a dopamine agonist to test the concept that long-acting agents might be associated with a reduced risk of dyskinesia and other motor complications.¹¹²⁻¹¹⁴ Each study demonstrated a significantly reduced risk of developing motor complications when patients are started with a long-acting dopamine agonist in comparison to a short acting formulation of L-dopa. These benefits persist even when supplemental L-dopa is added, although the frequency of

dyskinesia increases with the addition of L-dopa. Interestingly, patients assigned to start therapy with L-dopa had enhanced motor benefits on the UPDRS in each of these studies, even though open-label L-dopa could be added to patients in either treatment group if considered necessary. This has created some controversy in terms of whether it is preferable to initiate PD therapy with a dopamine agonist to reduce the risk of motor complications or to start with L-dopa to achieve an enhanced antiparkinsonian response.^{115,116} It also remains uncertain if comparable benefits could be achieved if patients were started on L-dopa and the agonist introduced at a later time point, and studies to test this concept are currently underway.

There is also evidence that the administration of dopaminergic agents in a more continuous fashion can reverse established motor complications. Several studies have demonstrated improvement in motor complications induced by oral formulations of levodopa after chronic infusion of apomorphine, lisuride, or L-dopa.¹¹⁷⁻¹²⁴ More recently, a prospective randomly ordered trial demonstrated a significant reduction in both *off* periods and dyskinesia with continuous subcutaneous infusion of lisuride compared with a standard oral formulation of L-dopa.¹²⁵

These observations support the notion that motor complications associated with the administration of L-dopa are related to the drug's short half-life and propensity to induce pulsatile stimulation of striatal dopamine receptors and not solely to features unique to the molecule itself. They further suggest that if oral formulations of L-dopa could be developed that provide less pulsatile, more constant stimulation of dopamine receptors, such treatment might provide the symptomatic benefits of the drug with a reduced risk of motor complications. Studies with continuous infusion of L-dopa support this hypothesis, although this approach is impractical for patients, physicians, and caregivers. The development of an oral strategy that extends the half-life of L-dopa and simulates the pharmacokinetic profile obtained with infusion therapy may permit patients to obtain the antiparkinsonian effects of L-dopa without the development of potentially disabling side effects. To test this treatment philosophy, two studies were carried out comparing the rate of dyskinesia production in patients randomly sorted to start treatment with the standard immediate release formulation of L-dopa or a controlled release formulation of L-dopa with prolonged bioavailability of the drug.¹²⁶ No difference in the frequency or time to onset of dyskinesia was detected between the two groups in either of these trials.¹²⁷⁻¹²⁹ Sinemet CR, however, has somewhat erratic absorption and was administered with a twice-a-day dos-

ing schedule, and may therefore have failed to avoid pulsatile stimulation. Another approach involves administering L-dopa in combination with a COMT inhibitor to extend its half-life and reduce the risk of the drug inducing pulsatile receptor stimulation. Indeed, preliminary studies in MPTP monkeys demonstrate that L-dopa administered four times daily in combination with a COMT inhibitor is associated with reduced dyskinesia and enhanced motor benefits in comparison to L-dopa alone.¹³⁰ Interestingly, this benefit was not seen with twice-a-day dosing, presumably because this schedule did not eliminate pulsatility.¹³¹ Studies to test this approach in PD patients are currently underway.

CONCLUSIONS

L-Dopa remains the most powerful and most widely employed drug in the treatment of PD. Questions regarding its potential toxicity and its role in the development of motor complications persist, but increasing evidence is beginning to shed light on these issues. There is little to suggest that L-dopa is toxic, based on laboratory studies. The effects of L-dopa in vitro can be attributed to experimental conditions and it is not certain that the toxicity seen in these models is relevant to the clinical condition. In vivo studies are for the most part negative and show no evidence of toxicity. The ELLDOPA study did not show clinical evidence of an adverse effect of L-dopa on disease progression, but the result may have been confounded by a L-dopa-induced long-term symptomatic benefit. Furthermore, imaging studies carried out as part of the ELLDOPA study showed that L-dopa is associated with an increased rate of decline of a biomarker of nigrostriatal function. Although this could represent a toxic effect, it might also relate to a direct pharmacologic effect of the drug on the dopamine transporter. The ELLDOPA study thus failed to clarify whether or not L-dopa is toxic in PD. With respect to the motor complications that accompany L-dopa treatment, increasing evidence indicates that they are related, at least in part, to the short half-life of the drug and its potential to induce pulsatile stimulation of dopamine receptors. It is thus possible to envision that administering levodopa in combination with a COMT inhibitor might permit more continuous and physiologic stimulation of dopamine receptors with a reduced risk of motor complications, although this remains to be established in PD patients.

Acknowledgements: The work was supported by an unrestricted educational grant provided by Novartis Pharma AG and Orion Corporation Orion Pharma. C.W. Olanow has served as a consultant to Novartis and Orion.

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