# Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson's Disease

I read the interesting report by Olanow et al.[1] regarding factors predictive of the development of levodopa (L-dopa)-induced dyskinesia and wearing-off in Parkinson's disease. L-Dopa has been widely used for more than 40 years, but a dose-finding study was never performed. I congratulate the authors for addressing this very important issue of L-dopa dosing. Their study provides scientific rationale for using as low a dose of L-dopa as clinically necessary for symptomatic control of Parkinson's disease while reducing dyskinesias and motor response fluctuations.

Although intravenous L-dopa was reported as effective in 1961,[2] oral therapy with this drug became possible only after a 1967 report by Cotzias et al.[3] based on a study of 17 patients. They used dihydroxyphenylalanine, DL-3,4-(alanine-1-14C) (D-L-dopa), "...because of the great expense of the L-compound."[3] The dose of D-L-dopa in most of their patients was 9 g or higher and was up to 16 g in some patients.[3] Soon, L-dopa became commercially available, but there was no clinical trial to establish the optimal dose. Neurologists used the L-dopa dose with which they felt comfortable.

Dyskinesia was the first motor complication of L-dopa observed by most experts.[4] On 6 g of L-dopa daily (equivalent to 1200 mg carbidopa–L-dopa [Sinemet; Merck & Company, Inc., Whitehouse Station, NJ]), 58% of patients had dyskinesias by the end of 6 months, and 75% had dyskinesias by the end of 1 year.[4]

We received authorization for L-dopa use as the second wave of neurologists in this field. As such, we had access to some of the observations made by others, and we witnessed severe dyskinesia in some patients on high L-dopa doses. The benefit/adverse effects profile did not seem to be favorable for L-dopa therapy. Therefore, we decided to use a lower dose and slower titration of L-dopa, targeting a dose of 3 g (Sinemet 600 mg) or lower. We reported our 12-year observations on low-dose L-dopa therapy in 1984.[5] The incidence of dyskinesia was markedly lower than reported by others.[4] By the end of 1 year, only 15% of our patients had dyskinesia, and only 3% had wearing-off or wearing-on/wearing-off.[5] We have continued to use a low dose of L-dopa. The incidence of both dyskinesias and motor response fluctuations in our longitudinally followed autopsy cases of Parkinson's disease was much lower compared with the incidence reported in most of the literature.[6] It is encouraging to see that an L-dopa dosing regimen similar to that started empirically in the late 1960s now has more robust data to support it. ■

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