ALL PD PATIENTS SHOULD START WITH LEVODOPA AND GO SLOW: YES

Fabrizio Stocchi
Institute of Research and Medical Care, IRCCS San Raffaele Rome Italy

Levodopa is the gold standard for the treatment of Parkinson's disease (PD), and no medical or surgical therapy has been shown to provide superior anti-parkinsonian benefits than can be achieved with levodopa. All patients suffering from PD eventually need levodopa. Moreover the appearance of dopamine agonists related side effects lead many physicians to use smaller dose of agonists and start levodopa sooner. Some patient needs levodopa as a first line drug because the severity of their symptoms at the time of the diagnosis. However, chronic levodopa treatment is associated with the development of motor complications (wearing off episodes and dyskinesia) in the majority of patients. Wearing off episodes reflect a loss of benefit following a levodopa dose prior to the onset of benefit from the next dose. Dyskinesias are involuntary movements that tend to occur at the time of the peak concentration and maximal levodopa benefit and are most often comprised of choreiform movements. In the extreme, patients may cycle between disabling dyskinesias during the on state and disabling parkinsonism during the off state. Indeed, motor complications are the primary reason for surgical interventions in PD. The development of a formulation of levodopa that provides the benefits of the drug without motor complications is a major unmet need in the treatment of PD.

A body of scientific and clinical evidence suggests that motor complications develop as a consequence of the intermittent administration of levodopa with non-physiologic restoration of brain dopamine due to the drugs short half life. It has been hypothesized that a more continuous delivery of levodopa might restore brain dopamine in a more physiologic manner, and reduce the risk of motor complications. Indeed, several studies have now shown that continuous infusion of levodopa in PD patients who experience motor complications is associated with a reduction in both off time and dyskinesia. However continuous levodopa infusion is cumbersome, and has not been employed to try and prevent the development of motor complications because it is not likely to be tolerated by patients with early PD. Accordingly, there has been a search for an oral levodopa treatment strategy that might mirror the pharmacokinetics of a levodopa infusion and provide the benefits of the medication without motor complications.

Entacapone is an inhibitor of catechol-O-methyl transferase (COMT) that extends the elimination half life of levodopa, and thus has the potential to provide more continuous availability of levodopa. In MPTP monkeys, levodopa plus entacpaone was shown to reduce both off time and motor dyskinesia in comparison to levodopa alone. Based on these considerations, the possibility that levodopa/carbidopa combined with entacapone (LCE) administered 4 times daily at 3.5 hour intervals might reduce the risk of dyskinesia compared with levodopa/carbidopa (LC) alone was tested in the STRIDE-PD study. The study failed to demonstrate the expected benefit. Indeed, patients randomized to receive LCE experienced an increased frequency of dyskinesia in comparison to patients receiving LC alone. We speculated that the study failed because administration of LCE 4 times per day at 3.5 hour intervals did not provide continuous dopaminergic delivery, as has subsequently been confirmed in pharmacokinetic studies. Further, the increased dopaminergic load associated with the addition of entacapone likely accounted for the increased frequency of dyskinesia in the LCE group. While the study failed to meet its primary endpoint, we were able to explore the data from the STRIDE-PD study to assess the role of levodopa dose and other risk factors in the development of dyskinesia and wearing off in this relatively long-term double blind trial.

The risk of dyskinesia in the total population was increased in a levodopa dose-dependent manner ($p<0.001$). Analysis using levodopa equivalent doses showed comparable results. Factors predictive of dyskinesia in rank order were: age at onset of PD, levodopa dose, weight, region, treatment group, gender, and UPDRS Part II. Risk of wearing-off also increased in a levodopa dose-dependent manner ($p<0.001$). Multivariate analyses showed similar predictors as dyskinesia, but included baseline UPDRS III, and excluded weight and treatment allocation.

Risk of developing dyskinesia and wearing-off each increased with higher levodopa doses. This study suggests that physicians should use the lowest dose of levodopa that provides satisfactory clinical control to minimize the risk of dyskinesia and wearing off.