ELLDOPA trial: Earlier versus Later Levodopa Therapy in Parkinson Disease

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Background: Levodopa is the most effective drug in ameliorating parkinsonian symptoms in Parkinson's disease (PD). However, long-term treatment with levodopa results in motor fluctuations, including dyskinesia and wearing-off. As denervation hypersensitivity was thought to be one of the mechanisms of this dyskinesia, it was presumed that levodopa hastens neurodegeneration by increasing oxidative stress. The ELLDOPA trail was designed to study the effect of levodopa on the rate of progression of PD.

Methods: This multicenter, randomized, double-blind, placebo-controlled trial was conducted in USA (33 centers) and Canada (5 centers) over a period of 3 years (Sept 1998 to August 2001). It was sponsored by NIH/NINDS.

Inclusion criteria: PD diagnosed in the last 2 years, age >30 years, H&Y stage <3, considered not likely to require treatment within 9 months from the enrollment period (because of mild symptoms).

Exclusion criteria: Patients actively on anti-parkinsonian medications, secondary parkinsonism, tremor severity >3 for any of the limbs in UPDRS, freezing of gait, postural instability, dementia, depression.

The patients were randomized to receive either placebo or Levodopa-carbidopa (L+C). Patients received levodopa in 3 different dosages (150 mg/d, 300 mg/d, and 600 mg/d). A total of 70 patients received placebo, 78 received 150 mg/d of levodopa, 82 received 300 mg/d of levodopa, and 81 received 600 mg/d of levodopa. Placebo or Levodopa was given for a total of 40-weeks, followed by complete discontinuation for 2-weeks (i.e., a wash-out period). The primary outcome measure was the change in the UPDRS scores from the baseline compared to that at week 42 (40-weeks of treatment + 2-weeks of washout). A subset of the subjects had undergone a dopamine transporter scan (DAT-SPECT) as the investigators received funding for this several months after the initial recruitment.

Results: Of the 361 subjects enrolled in the study, 317 (88 %) took the study medication for 40 weeks, and 311 (86 %) completed the 2 weeks of washout. Overall, in terms of the primary outcome, Levodopa was NOT associated with any worsening of the UPDRS scores at the end of 42-weeks. As mentioned above, 70 patients received placebo, 78 patients received 150 mg/d, 82 patients received 300 mg/d, and 81 patients received 600 mg/d of levodopa. The total UPDRS score changed by a mean of 7.8 ± 9.0 points in the placebo group whereas the change in the 150 mg/d, 300 mg/d, and 600 mg/d groups were 1.9 ± 6.0, 1.9 ± 6.9, and -1.4 ± 7.7, respectively. The UPDRS-motor score changed by 5.2 ± 6.4 in the placebo group, whereas the change in the 150 mg/d, 300 mg/d, and 600 mg/d groups were 1.4 ± 5.5, 1.4 ± 5.3, and -1.4 ± 5.9, respectively. There was a significant difference between the change in the UPDRS scores in the placebo group and levodopa groups overall.

Regarding the DAT-SPECT scan data, the percent decrease in striatal [^{123}I] Beta-CIT uptake in the SPECT scan over the 40 weeks of the study treatment was greater among subjects in the levodopa groups than in the placebo group, but this difference was not statistically significant. However, the reason was unclear, and the authors speculated that long-term treatment with levodopa could have some effect on DAT density (such as downregulation of dopamine transporters due to chronic levodopa therapy).

Conclusions: From a clinical perspective, this study did not show any hastening of the progression of PD with the use of levodopa. High doses of levodopa were, however, associated with a greater frequency of adverse events such as dyskinesia. The authors recommended customizing the dose of levodopa to the needs of the individual patient based on the clinical response and the profile of adverse events.

Additional Reading, if interested:

Verschuur CV, et. al; LEAP Study Group. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. N Engl J Med. 2019, 380(4):315-324.

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