CAN LEVODOPA DELIVERY BE IMPROVED: NO

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Levodopa with carbidopa is undoubtedly the gold standard of treatment for Parkinson's disease. But an initial spectacular benefit with this drug, known as the honeymoon period, is often compromised within a few years by the occurrence of disabling fluctuations and dyskinesia. The reasons for this switch are poorly understood, but probably involve pharmacokinetic factors, including the erratic absorption and short elimination half-life of levodopa combined with pharmacodynamic post-synaptic changes, resulting from the abnormal pulsatile stimulation of the system by the drug.

Several attempts in the past with purported controlled-release formulations of levodopa proved disappointing. In the recent years though, new extended release formulations, and novel delivery strategies (nanoparticles, transdermal, nasal, etc.) have been developed and some of them tested in patients, reigniting the hope for successful improved levodopa delivery.

LD methylester (ME) is a highly soluble prodrug that provides a more rapid and consistent absorption and therefore, more rapid onset of action versus standard oral LD preparations, while the half-life of the two preparations is similar. In a randomized trial, comparing the effectiveness of methylester with standard LD in 221 patients with advanced PD, the total daily off-time between the two groups was not statistically significant[1].

IPX066, is a new oral extended-release formulation of carbidopa-levodopa, which has already completed two randomized phase III clinical trials.

In the first study, applying a complicated double-blind randomized switch design in 393 patients, Hauser et al., showed that IPX066 reduced off -time by approximately 1 h per day compared with standard immediate-release carbidopa/levodopa[2]. Certain methodological issues relating to the long and complex process to switch patients from immediate-release carbidopa-levodopa to IPX066, are of concern. In addition, patients still endured nearly 4 h of off -time after switching to IPX066, which can still greatly affect everyday life of patients. Indeed the described benefit was not reflected in the quality of life ratings.

The second, recently published, is a smaller double-blind, randomized study of IPX066 in patients with fluctuating PD. The study used a crossover design with two double-blind 2-week periods interrupted by a 1-week open-label wash-out period, during which all patients were treated with IPX066[3]. During double-blind treatment, there was a statistically significant difference, with 8.5% less OFF time on IPX066 versus LCE. Again the benefit was not reflected in quality of life ratings.

A new combination of fixed doses of carbidopa, regardless of L-dopa dose strength, has been tested in a proof-of-concept phase II study in 117 patients with fluctuating PD[4]. This trial compared traditional formulations of LD/CD 4:1 plus 200 mg of entacapone (LCE) with LCE tablets that contained a fixed amount of either 65 or 105 mg of carbidopa. A statistically significant reduction of daily OFF time of approximately 30 min was found from baseline to end of treatment with both doses of carbidopa, compared to standard treatment.

A novel nitrocatechol compound with potent inhibitor effects on COMT has entered phase III clinical trials. Opicapone (BIA-9-1067) is associated with long-lasting inhibition of COMT for more than 24 hours after a single dose. A recent trial included 407 PD patients on chronic L-dopa therapy and exhibiting motor response oscillations[5]. Subjects were randomized to receive 25 or 50 mg of opicapone once-daily versus placebo over 14 weeks of double blind treatment. There was a reduction of total daily OFF time with opicapone 50 mg of approx. 30 min comparing to placebo.

Another newly developed COMT inhibitor, nebicapone, has been tested in Phase III clinical trials. Nebicapone significantly decreased the mean daily 'off'-time compared with placebo and entacapone 200 mg[6]. However, the observation that 4/200 exposed to this treatment presented increased liver transaminases raised significant concerns.

XP21279 is a novel L-dopa prodrug that is absorbed from the small and large intestine. It is rapidly metabolized to L-dopa after absorption. The capacity for colonic absorption provides extended plasma concentrations. XP21279 was recently studied in a small double-blind crossover trial in 28 patients with fluctuating PD, in comparison to immediate-release LD/CD[7]. Double-blind treatment periods lasted for 2 weeks, and there was no statistically significant difference between XP21279 and standard LD/CD.

DM-1992 is an LD/CD bilayer tablet formulation combining immediate- and extended-release layers within a polymer-based gastroretentive drug delivery system. An open-label, randomized, cross-over study, in 34 PD patients with chronic L-dopa therapy and motor response oscillations, compared DM-1992 to immediate-release LD/CD using two 10-day treatment periods separated by 1-week washout[8]. Patient diaries showed a marginal decrease of 5,3 % in daily OFF time with DM-1992 versus LD/CD immediate release (P=0.047).

Nanotechnology, allowed drugs to be manipulated into nanoscale sizes for delivery to different parts of the body, at the same time, retaining the valuable pharmacological properties of the drugs. However, efficient drug delivery and excellent release potential of these delivery systems may be hindered by possible untoward side effects. In a preliminary study, the sub-acute toxicity of oral zinc aluminium nanocomposite with and without levodopa was assessed in orally treated rats[9]. Aspartate aminotransferase (AST) in levodopa nanocomposite, was notably elevated compared to controls. In addition the kidneys of treated rats with levodopa nanocomposite were found to have inflammatory changes, with leukocyte infiltration around the glomeruli. The observed result has suggested possible liver and renal toxicity in orally administered levodopa intercalated nanocomposite.

In conclusion, the methods for improved levodopa delivery tested in clinical trials so far, are far from being impressive, and cannot be considered the major breakthrough that many are expecting. The published results do not seem to offer greater clinical efficacy over what is known from treatment with the existing available COMT or MAOB inhibitors.

The long hope for improved non invasive levodopa delivery continues therefore to be a major unmet need in 2015.

References

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