

## **CAN LEVODOPA DELIVERY BE IMPROVED: YES**

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Levodopa (LD) was developed as a means to restore striatal dopamine levels and it is considered the gold standard for the symptomatic treatment of Parkinson's disease (PD). Unfortunately, LD usage remains associated with both acute and chronic side effects that could compromise long lasting treatment. LD has many pharmacokinetic properties that may limit its effectiveness. First of all LD is characterised by a particularly short plasma half-life (1-1.5 hours), chemical instability (oxidation), enzymatic instability (decarboxylation). Many factors (endogenous, exogenous, iatrogenic) can also limit the gastrointestinal absorption of LD (gastric pH, the fullness in the stomach, amino acids and lipids in diet and the time it remains exposed to the degradation activity by gastric mucosa).

The long term LD therapy leads to motor complications, involving motor fluctuations (wearing-off, delayed-on, on-off) and dyskinesias (off-period dystonia, diphasic dyskinesia, peak-dose dyskinesia). These occur in about 50-80% of PD patients, who received LD for more than 5-10 years. Motor complications represent a major cause of disability of the patient; in extreme cases they can lead to a situation of alternation between ON complicated by severe dyskinesia and OFF with disabling parkinsonism (1). The origin of motor complications is primarily due to alterations of dopaminergic transmission and it is known only in part: the use of standard LD is associated with a fluctuating and pulsatile stimulation of striatal dopaminergic system, a system physiologically characterized by a tonic activity (2). Thus LD chronic therapy plus progressive striatal dopaminergic denervation can determine alterations of the basal ganglia function, with modifications of the receptor plasticity characterized by the simultaneous appearance of phenomena of tolerance (short duration response to LD) and sensitization (dyskinesias). Therefore, pharmacokinetic and pharmacodynamic factors that modify the availability of central dopamine, acquire singular importance.

Over the years, clinical and experimental research aimed to limit some of the pharmacokinetic and pharmacodynamic factors, and in particular to produce a more easily absorbable levodopa. Ongoing clinical and preclinical research has led to the discovery of promising new therapeutic strategies that might prevent or reduce motor complications. Available controlled release levodopa formulations produce more sustained plasma levels but also show lower bioavailability and slower time to peak, resulting in poor clinical outcome especially in advanced patients. Recent levodopa delivery formulations include duodenal infusion of a levodopa/carbidopa, new extended-release levodopa and oral pro-levodopa forms. The duodenal infusion of a water-soluble suspension of levodopa and carbidopa in methylcellulose (levodopa/carbidopa intestinal gel, LCIG), has been found to be successful to achieve stable plasma concentrations of levodopa. Drug administration includes a morning dose (100–200 mg in 10–30 minutes) and a maintenance dose (typically 40–120 mg hourly during the waking hours) according to patients specific need. Many open-label clinical trials have consistently documented a significant reduction in motor complications, a benefit on non-motor symptoms and significant improvements in quality of life (3).

IPX066 is a novel mixed immediate release (IR) and sustained-release levodopa preparation designed to prolong the clinical effect of a single dose. In patients with advanced PD, it provided a rapid onset of clinical effects, which lasted for approximately 6 h after a single dose. Pharmacokinetic studies demonstrate similar time to peak dose as regular IR L-DOPA, but a longer duration of time with > 50% of peak dose. Clinic trials in fluctuating PD patients show that IPX066 provided more 'on' time despite fewer daily doses, compared to IR L-DOPA. As expected, it was also superior to placebo in early PD. However, it is not known whether it can achieve L-DOPA levels that are continuous enough to delay the onset of fluctuations when given early in the disease (4).

Novel delivery systems such as inhaled levodopa or transdermal levodopa micropumps are also currently being investigated for efficacy with promising future perspectives. Encouraging results are arrived from the positive phase 2 trial results for an inhaled formulation of levodopa, CVT-301. When administered to patients in an "off" state, it provided a rapid improvement in motor function;

following intrapulmonary delivery, levodopa is more rapidly absorbed and plasmatic concentration is less variable. It is designed to work as needed drug taken in conjunction with the oral L-dopa therapy (5).

Some positive results come from the levodopa/carbidopa “pump-patch” designed to continuously deliver liquid formulations of the drug (ND0612H and ND0612L) subcutaneously. It consists of a device, made up of a reservoir where the drug is stored, and a series of painless micro-needles which pump the therapy under the skin and into the blood stream, exploiting a chemical diffusion of a drug. In the recent results of the Phase II trial it demonstrated to led to stable and clinically-significant plasma levodopa levels.

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