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LEVODOPA 2.0: NEW STRATEGIES TO EVEN OUT THE PEAKS AND VALLEYS

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ABSTRACT

There's bad news and good news for the Parkinson's community: Parkinson's disease is on the rise, but so are better treatments.

For almost 50 years, we've relied on levodopa as the gold standard of symptomatic therapy of Parkinson's disease (PD). Within this standard, Sinemet (carbidopa/levodopa) is the most commonly prescribed medication, and for good reasons: it is safe, well-tolerated and effective for motor symptoms. Like every drug, though, levodopa has potential side effects, the hallmark being motor fluctuations. A desire to capitalize on the benefits and avoid these adverse effects has fueled research into new versions of the drug.[1,2] Earlier this year, two new formulations of levodopa were approved, and several others are in mid-to-late stages of clinical testing.

Until the as-yet elusive curative therapy for PD is realized, we must continue to develop better symptomatic therapies and refine those, like levodopa, that are currently available.

Levodopa as We Currently Know It

Levodopa markedly improves motor symptoms for the majority of people with Parkinson's disease. This leads to improvements in general quality of life and performance of daily activities, which in turn allows independence to be maintained and employment to be extended.[3] Furthermore, widespread use of levodopa has decreased overall mortality and morbidity in the Parkinson's population.[3]

Still, for all the good this medication imparts, it has its limitations. For one, it unfortunately does little for the non-motor symptoms of PD. Secondly, as a consequence of its short half-life, levodopa requires frequent dosing. Even in conjunction with carbidopa, a decarboxylase inhibitor that prevents peripheral breakdown, the half-life is a mere 90 minutes and the duration of action only three to four hours. Finally, this recurrent cycle of medication kicking in and then wearing off with each administration leads to oscillations in plasma drug concentrations that, with chronic use (five to 10 years), contribute to motor complications in a good number of patients.[4] Additional causative factors include higher total daily dosages of levodopa; the drug's pulsatile, non-physiologic stimulation of degenerating neurons; and longer duration of PD.[1,2] Motor complications include both motor fluctuations (alterations between "on" periods of good mobility and "off" periods when

medication response is suboptimal) and dyskinesia (involuntary movements that arise most commonly at peak levodopa effect).

While these side effects can be disabling and debilitating,[4] many people tolerate the medication quite well. Common problems—nausea and lightheadedness (due to orthostatic hypotension)—can often be managed with dosing or behavioral alterations. Taking levodopa with a carbohydrate snack, extra carbidopa (Lodosyn) or even domperidone (a peripheral dopamine antagonist available outside the United States) may combat nausea. If orthostatic hypotension is an issue, drinking more water, wearing compression stockings and elevating the head of the bed are initial steps that may be taken to counter dizziness and lightheadedness. Other approaches may include liberalization of dietary salt intake and adjustment of high blood pressure medications, which can be done in conjunction with the patient's primary care doctor or cardiologist.

Levodopa itself is quite safe; it poses only a handful of possible pharmacological interactions and most of them are fairly benign. Vitamin B6 can lessen levodopa's efficacy, and iron supplements may affect its absorption. Protein can also interfere with medication absorption, especially in patients with motor fluctuations. Since levodopa is an amino acid, it competes with other amino acids—from dietary protein—for uptake in the proximal small intestine.[5] This, in addition to peripheral decarboxylation and delayed or inconsistent gastric emptying, can result in erratic absorption and bioavailability. For maximal benefit, levodopa should be taken 30 minutes prior to or 60 minutes after a meal. When scheduled every few hours, this instruction can generate frustration and noncompliance on the part of the patient.

A Brief History of Levodopa Therapies

Throughout the 1960s, different administration routes and dosages of levodopa were tested in clinical trials. Once the safety, tolerability and efficacy of high-dose oral administration were demonstrated, levodopa was FDA-approved for use in PD in 1968. A few years later, in 1973, Sinemet was released. It wasn't until 1991 that controlled-release Sinemet (Sinemet CR) came out. Almost 20 years following that, in 2010, Stalevo (carbidopa/levodopa and entacapone) reached pharmacy shelves.[6] The latest developments in the United States occurred in early 2015 when two new formulations of carbidopa/levodopa—Rytary and Duopa—were approved. The latter has been available in Europe under the name Duodopa since 2004.

Improving Upon an Old Standard

New drugs are always met with a combination of excitement and apprehension. Some patients and physicians are eager to try the "next best thing" while others choose to stick with what they know. Regardless of which camp one falls into, everyone would agree that having more treatment options, whether or not they are utilized, is preferable. This is especially true in a disease like Parkinson's where advancing symptoms, medication side effects and comorbidities can restrict alternatives.

Rytary

Each capsule of Rytary contains immediate and extended-release beads of levodopa in a 4:1 ratio with carbidopa. Four different dosage strengths, ranging from 23.75/95 mg to 61.25/245 mg carbidopa/levodopa, are offered. The immediate-release beads take action in approximately 30 minutes and the sustained-release ones last four to six hours. The latter facilitate less frequent dosing (typically three, but up to five, times per day) and a steadier plasma levodopa concentration. Because higher total daily dosages of levodopa are recommended when switching from Sinemet IR or CR, three to four capsules of Rytary are often prescribed at each dosing administration.[7]

Although levodopa-naïve patients can take Rytary,[8] the most common users will probably be those with advancing disease who have inadequate control or motor fluctuations on their current regimen. In clinical trials evaluating Rytary, patients with motor fluctuations experienced reduced frequency of levodopa dosing and at least one less hour of "off" time per day.[9] Patients who have difficulty swallowing pills will be able to take advantage of the fact that the capsule contents can be sprinkled onto applesauce or foods of similar consistency for consumption.

Greater patient and physician experience with Rytary will hopefully suggest the optimal titration and dosing schedule. Time will tell whether the formulation is truly able to lessen motor complications in the long run.

Duopa

Duopa is a gel suspension of carbidopa and immediate-release levodopa. It is designed for direct intestinal infusion through a percutaneous endoscopic gastrojejunostomy (PEG-J) tube. As its absorption is not affected by gastric mobility or emptying, more stable plasma levodopa concentrations can be achieved.

It is indicated for individuals with advanced PD who remain levodopa-responsive but suffer motor fluctuations.[10,11] Various studies

of this medication in advanced patients have shown a decrease in daily "off" time, gait dysfunction and freezing, along with improvements in non-motor symptoms, quality of life, dyskinesia severity, and "on" time without disabling dyskinesia.[12] In those with three or more hours of "off" time per day, Duopa decreased "off" time and increased "on" time without dyskinesia by an average of four hours per day each.

This new formulation may be an option for those who do not want deep brain stimulation or cannot undergo the procedure because of significant postural instability, cognitive impairment or medical comorbidities. Those over the age of 70, who may get a less robust response from DBS, might also consider Duopa. The drug can be employed in people with mild to moderate dementia (MMSE > 20), although this necessitates a responsible caregiver to administer medication and PEG-J tube care. Duopa can also be provided via a nasojejunal (NJ) tube on a short-term basis (e.g., when a patient cannot tolerate oral intake for a temporary but extended amount of time) or for a trial period to evaluate drug response before committing to long-term therapy.

In order to start Duopa, patients must first transition to oral, immediate-release Sinemet. They must also undergo PEG-J tube placement—an outpatient procedure performed by a general surgeon, radiologist or gastroenterologist under moderate sedation or local anesthesia. Once the tube is in place, a cassette of Duopa, which contains 2000mg levodopa and 463mg carbidopa, is attached to a pump programmed to deliver a single morning dose, a continuous 16-hour infusion, and extra 20mg levodopa doses up to once every two hours as needed for rescue therapy of acute "off" periods.[12]

In addition to the well-known side effects of levodopa, Duopa presents risks associated with the device itself, including malfunction, infection and intestinal complications (ileus, ischemia, hemorrhage, obstruction and perforation). One study showed the greatest rates of discontinuation were due to stoma infection or worsening dyskinesia not manageable with infusion reduction; these issues were highest among elderly patients and in the first year after the implant.[13] Another trial noted an association between Duopa and a subacute or chronic sensory or sensorimotor axonal polyneuropathy. While this neuropathy has not been conclusively linked to vitamin B12 or folate deficiency, it's worthwhile to measure these levels prior to starting Duopa and at regular intervals during therapy.

As with any new drug, time and experience will direct appropriate prescribing and will reveal the most common side effects and benefits.

New Frontiers in Motor Symptom Treatment

While clinicians fold these new offerings into their arsenals, researchers are working toward other formulations to control, and possibly even prevent, motor fluctuations.

Liquid Levodopa

ND0162L is a liquid formulation of carbidopa/levodopa that is delivered subcutaneously through a belt pump system similar to an insulin pump. A "pump patch" (an adhesive patch that delivers medication subcutaneously through microneedles) is also in parallel development. Fixed doses of the medication are infused over a 24-hour period, with lower dosages provided in the overnight hours.

This drug will likely be designated for patients with moderate to severe PD. Given the around-the-clock delivery, ND0162L may particularly benefit patients who struggle with frequent nighttime awakening due to Parkinson's symptoms or who have pronounced difficulties upon awakening in the morning secondary to wearing off.

A Phase II trial in patients who had Parkinson's for an average of eight years and had developed motor fluctuations demonstrated a high steady-state plasma levodopa concentration, reduction of motor fluctuations and a mean decrease in "off" time of two hours.[14] ND0162L is entering Phase III testing and could reach patients as early as 2018.

Higher dosages of liquid carbidopa/levodopa (ND0162H) are also being trialed in more advanced patients; this therapy will likely represent an alternative to current surgical interventions and Duopa.

Rescue Therapies for Sudden "Off" Periods

Rescue drugs for sudden, unpredictable "off" periods are sorely lacking. The only FDA-approved drug—the dopamine agonist apomorphine (Apokyn)—is given via subcutaneous injection. It can cause orthostasis, nausea and vomiting, and requires pre-treatment with anti-emetics and test-dose monitoring in the physician's office. Even when tolerated, however, injections can be impractical to self-administer in the midst of an "off" period.

Two rescue drugs, described below, are in Phase III testing and could come to market as early as 2016.

APL-130277: The effects of this sublingual thin-film strip of apomorphine are seen in approximately 10 minutes and last up to 90

minutes. It has a lower incidence of nausea and hypotension than the injection and is much more easily administered. It has been tested at 10, 15 and 25mg doses.

CVT-301: Motor symptom relief from these capsules of levodopa inhalational powder, administered via a device similar to an asthma inhaler, occurs in about 10 minutes and lasts up to 60 minutes. Scientists are currently testing 35mg and 50mg doses. Of note, this therapy is solely levodopa—a patient must therefore be on concurrent carbidopa/levodopa or Lodosyn to prevent peripheral breakdown and side effects.

Despite these advancements, challenges with levodopa remain. For now, though, we have additional tools at our disposal and several more in the pipeline which will allow us to fine-tune the management of Parkinson's symptoms and enable our patients to enjoy the best quality of life possible.

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The Michael J. Fox Foundation is the largest nonprofit funder of Parkinson's disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson's disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson's today. Because patients are vital partners in this process, the Foundation works to mobilize volunteer engagement in research by providing education and direct research-related services to Parkinson's clinicians, researchers, patients and families.

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