Shining A Light On the Off Periods of Parkinson's Disease

New formulations for rescue from the off period are coming.

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Introduction

Parkinson's disease (PD)—the second most common neurodegenerative disease—is a progressive disorder that results from loss of dopaminergic neurons. Although the densest region of loss is in the substantia nigra pars compacta causing significant motor function deficits, it is important to remember that dopamine is ubiquitous.[1,2] Dopamine is implicated in coordinating movement, mood, and memory; dysregulation in this system causes symptoms in those areas. These are grouped into the motor and nonmotor symptoms of PD. Treatment therapies have traditionally focused on motor symptoms since the first pharmaceuticals specific for treatment of patients with PD were introduced in the 1960s.[3] Motor symptoms include tremor, bradykinesia, stiffness and rigidity, limited mobility, and postural instability. Nonmotor symptoms include autonomic instability, dementia, anxiety, and gastrointestinal dysfunction; these can have just as much impact on patients as the motor symptoms, if not moreso.[4,5] In 2010, there were approximately 630,000 cases of PD in the US, which is predicted to double by 2040.

Current treatment strategies have focused on increasing the amount of dopamine and dopamine activity within the midbrain. The gold-standard therapy, levodopa, is a dopamine precursor. Evolution of therapy has not been directed at finding new dopaminergic compounds but rather at changing the delivery of levodopa to avoid fluctuating plasma drug levels that cause the on-off phenomena for the patient,[3] which is the rate-limiting step in prolonged use of levodopa.

Long-term levodopa treatment of patients with PD commonly leads to off periods described as either predictable or unpredictable fluctuating dyskinesias (ie, hyperkinetic movement) or akinesia (ie, lack of movement).[6] Although most clinicians can appreciate this narrowing of the therapeutic treatment window over time, the pathophysiology is poorly understood. A leading theory is that because dopamine signaling is ubiquitous, the location of dopamine loss matters. For motor symptoms, if there is predominantly posterior putaminal striatal nigrostriatal terminal loss and disruption in normal phasic signaling it will prevent uptake of the precursor levodopa, limiting conversion to dopamine and reliable release, resulting in the motor effect waxing and waning. Compounding this effect, the dopamine in the synapse is cleared more slowly because there are fewer terminals for reuptake; this would then lead to an inconsistent stimulation effect on sensitized dopamine receptors.[7] This is not an academic problem seen in the lab, 40% of real-world patients with PD experience off periods after 4 to 6 years of treatment, and 90% of patients with PD experience off periods after 9 years of treatment.[6]

To avoid these on-off periods, other treatments have been introduced to increase the duration of availability and efficacy of levodopa without titrating the dose; these include compounds with mechanisms such as monoamine oxidase B inhibitors, catechol-*O*-methyltransferase inhibitors or activating dopaminergic receptors via dopaminergic agonists.[6] These adjunctive treatment options are now being used as alternative monotherapies for patients with early PD. It should also be noted that the very first medicine used to treat people with PD, amantadine, is now used more often for the management of dyskinesia symptoms, although it has no known direct effect on dopamine or dopamine receptors.

Current Issues with Treatment

Current treatments for controlling off periods are via a conventional oral route, and approximately two-thirds of

time spent in the off period is because of waiting for treatment to turn on.[6] This has been attributed to a number of mechanisms, including gastric motility issues associated with PD itself—if it takes longer for medication to reach the gut where it is absorbed, it will take longer to have any symptomatic benefit. Another potential mechanism could be the loss of the phasic signaling related to where the dopaminergic neuron loss is most prevalent.[7] Adjunctive medications often require frequent ingestion to help with the on-off periods which can be difficult for some patients with PD for whom the pill burden cannot be understated

Drugs delivered orally are also affected by metabolism and this is especially true of dopamine agonists that have been traditional adjunctive therapy to levodopa. Many oral medications, especially ropinirole undergo extensive hepatic metabolism via cytochrome P450 enzymes. Only 10% of orally ingested ropinirole is excreted unchanged by hepatic metabolism.[8]

Apomorphine is an alternative as it is available as a subcutaneous injection; it is a potent dopamine agonist that activates all dopamine receptors. Apomorphine also binds to serotonin receptors and α-adrenergic receptors. Once injected, apomorphine provides rapid relief in 7 to 10 minutes and has a half-life of 40 minutes, making it an ideal rescue medication.[9] Subcutaneous administration of any drug can be painful, inconvenient, and difficult to administer, however. Because dexterity and tremor of PD affect patients' fine motor skills, if a caregiver is not available to assist, apomorphine may not be a viable option, and this can lead to treatment nonadherence.

Spotlight on Emerging Therapy

Intranasal drug delivery can bypass the blood-brain barrier (BBB) and nanotechnology is being used with selegiline and ropinirole to deliver these adjunctive treatments. A study using chitosan nanoparticles for pramipexole dihydrochloride has shown that some of these nanoparticles can diffuse across artificial membranes that resemble the BBB at percentages as high as 93.32%.[2] The particles are very small and easily entrapped by cells; studies show entrapment efficiency of 292.5 nm+/- 8.80 at percentages as high as 91.25%.[2] A similar study showed intranasal administration of selegiline and chitosan nanoparticles to rats delivered 20-fold higher plasma concentrations and 12-fold higher brain concentrations of selegiline compared to rats given selegiline orally.[10] The higher concentrations of these medications within the brain and increased uptake by cells leads to increased dopamine activity and better performance in locomotor activity.

Another investigational intranasally delivered therapy is CVT-301, which is a dry powder intranasal formulation of levodopa. Like the other medications discussed, it is being studied for use managing symptoms of off periods. Absorption of CVT-301 occurs in the lungs, avoiding gastrointestinal metabolism.[11] In a 12-month randomized, placebo-controlled, double-blind study, treatment with CVT-301 significantly improved patients' off-period symptoms. At week 52 of the study, 85% of patients treated achieved an on state that lasted at least 1 hour after taking CVT-301; 75% had some kind of improvement in motor function.[a] Patients and providers need to be educated on the mechanics of this delivery system, which is a pump, not an inhaler, that requires assembly for use. An oval pod containing the medication is placed in the pump, which is then squeezed to puncture the pod and aerosolize the medication for inhalation. Because the dose is 2 sprays, this process needs to be performed twice to deliver a single dose.

Sublingual drug administration is also being considered for treatment of patients with PD. Orally dissolving films provide rapid drug administration and absorption and bypass first-pass metabolism.[6] Sublingual administration is considered an easy and simple way for a patient to absorb medication without drinking water.[12] For patients with dysphagia, the frequent administration of as-needed medications like ropinirole, which has a short half-life, can be difficult and taxing. An in vivo pharmacokinetic study tested delivery of ropinirole in a sublingual film formulation and found that the ropinirole reached systemic circulation within 15 minutes and had significantly high bioavailability in comparison to oral formulations.

A sublingual form of apomorphine, APL-130277, is in clinical development for treatment of off-period symptoms and uses a bilayer strip with apomorphine in one layer and a buffer in the other to help control the pH and avoid skin or mucosal irritation. The strip is placed under the tongue for 2 to 3 minutes.[3] A proof-of-concept study assessed efficacy of this apomorphine strip and found that 78.9% of treated patients achieved full on response in 30 minutes or less, and 40% of the patients achieved full on response within 15 minutes. The mean duration of post-treatment on time was 50 minutes.[6] It is important to note this is not a dissolvable strip and may not be swallowed. The strip is stiffer, varies in size from a penny to a quarter, and may need to be folded, placed, and held under the tongue for 2 minutes, during which time the patient may not swallow.

Both the intranasal and sublingual formulations are to be available in late 2018 or early 2019.

Conclusions

Patients with PD face an arduous task of adjusting levodopa dosing and timing to maintain themselves in an on state. Patients with chronic PD require rapid-acting

a Efficacy and safety study of CVT-301 in Parkinson's disease patients with off episodes (NCT02240030)

medications to provide rescue from an off to an on state. Current therapies and emerging therapies focus on the motor symptoms of the off period (eg, rigidity, tremor, bradykinesia), yet because dopamine is ubiquitous there are other symptoms (eg, anxiety, autonomic dysfunction, and balance) that also need to be better understood. More research is needed regarding how these medications impact all off-period phenomena. The current mainstay treatment is apomorphine administered subcutaneously. Subcutaneous administration, while an effective but underutilized medication, has limitations for patients with chronic PD and frequently requires help to administer. New rescue strategies are being developed to help make administration easier and less painful, with similar onset of action. Sublingual films and intranasal sprays may have a bright future in the treatment landscape for patients with PD. ■

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