Parkinson's Rotigotine Patch Treatment Approved

BY ELIZABETH MECHCATIE
Senior Writer

For the first time, a transdermal drug delivery system is available for treating Parkinson's disease patients, a treatment option that provides both practical and theoretical benefits for this population, according to experts not involved in clinical trials of the product.

Last month, the Food and Drug Administration approved a transdermal patch containing rotigotine, a nonergotamine dopamine agonist previously not available in any form in the United States, for the signs and symptoms of early-stage idiopathic Parkinson's. Approval was based on three randomized, double-blind, placebo-controlled studies of 1,154 patients with early Parkinson's, who were not on other drugs for Parkinson's. The patch will be marketed as Neupro by the German company Schwarz Pharma LLC and should be available by June 22-30. At press time, price was not available.

A transdermal delivery system is one clear advantage for patients already taking many pills, said Dr. David Standaert, professor of neurology and director of the division of movement disorders at the University of Alabama at Birmingham. The pharmacology of rotigotine is a little different from that of the most widely used dopamine agonists, pramipexole and ropinirole, but the main difference is the transdermal system, he said in an interview.

Another advantage is that the continuous delivery of medication over 24 hours provides a stable blood level, he said. Research suggests the peaks and troughs with conventional dopaminergic drugs may cause some of the problems associated with oral therapy—end of the dose "wearing off" and dyskinesia—and possibly hallucinations and neuropsychiatric effects. However, there is no evidence that the steady level provided by the patch will translate into long-term clinical benefits. Dr. Standaert, who also is the director of the university's Center for Neurodegeneration and Experimental Therapeutics, was not involved in rotigotine studies. He has no financial ties to the manufacturer but has consulted on the pharmacologic properties of rotigotine to UCB, the U.S. pharmaceutical company that is in the process of acquiring Schwarz Pharma.

"There are a lot of both theoretical and practical advantages to finally having patch therapy for Parkinson's," agreed Dr. Michael Pourfar, a neurologist in the division of movement disorders, at North Shore University Hospital, Manhasset, N.Y. Because there are effective dopamine agonists available for Parkinson's, he said he would not want patients to feel like they must switch medications. "But I do think this is something that will improve quality of life for many," he added in an interview, noting that for some, the patch could replace as many as six pills per day. He has not been involved in trials of rotigotine and has no financial ties to the maker.

Rotigotine is delivered continuously though the silicone-based patch that is applied to clean, dry intact skin and is replaced every 24 hours. It is available in three strengths: 2 mg, 4 mg, and 6 mg/24 hr. The recommended dosing is to start at 2 mg. When additional therapeutic effects are needed, the dose may be increased weekly by 2 mg/24 hours if tolerated, according to the package insert. In studies, the lowest effective dose was 4 mg/24 hours, and in dose-ranging studies, doses above 6 mg/24 hours were not more effective and were tied to a higher rate of adverse reactions.

The patch should be applied to the front of the abdomen, thigh, hip, flank, shoulder, or upper arm at about the same time every day, avoiding same-site reapplication more than once every 14 days.

The change from baseline for the combined scores for the activities of daily living and motor components of the Unified Parkinson's Disease Rating Scale (UPDRS) was the primary outcome in the three studies, which enrolled early-stage Parkinson's disease patients not on dopamine agonist treatment, whose mean age was 60-63 years.

In one trial, a 28-week multicenter North American study, 277 patients received up to a 6 g/24 hours dose of rotigotine or placebo. The mean reduction in the combined UPDRS score from baseline was 4.0, versus a mean 1.39 increase from baseline among those on placebo, a statistically significant difference of 5.3. The most common side effects were dizziness, nausea, vomiting, drowsiness, and insomnia, "most of which are typical for this class of drugs," said the FDA. Nearly 40% had application site reactions—mostly mild or moderate—versus 14% of those on a placebo patch. The delivery system contains a sulfite that may cause allergic reactions in sulfite-sensitive people.

The patch is not yet approved for advanced disease, but in a recently published, placebo-controlled, 24-week study of 351 patients with advanced Parkinson's, those treated with two doses of the patch had significant reductions in daily "off" time than those on placebo (Neurology 2007;68:1262-7). ■

Infections, Drug Changes Cause the Biggest Problems for PD

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

BOSTON — Drug changes—by the physician or the patient—and infections are the most likely culprits behind motor fluctuations that land a patient with Parkinson's disease in the emergency department.

"The first thing to do is look for infections or other medical issues, and check to see if there have been any medication changes," said Dr. Stewart Factor said at the annual meeting of the American Academy of Neurology.

Urinary tract or upper respiratory infections can trigger dyskinesias by altering the sensitivity to medication, said Dr. Factor of Emory University, Atlanta.

He cited the case of a 60-year-old woman whose "off" periods confined her to a wheelchair. She had sudden rapid cycling from virtual immobility to severe dyskinesia that made it difficult to breathe, and reported a fever of 101° F for 3 days. In the ED, she displayed decreased breath sounds and crackles on the left side. A chest radiograph confirmed lower left lobe pneumonia. She responded well to intravenous antibiotics and fluids, but the dyskinetic cycling continued despite holding her carbidopa-levodopa and decreasing her pergolide by half. Only after 48 hours, when she became afebrile and the pneumonia had improved, was it possible to restart her medication, Dr. Factor said.

A second patient arrived at the ED short of breath, dehydrated, and diaphoretic, with a sudden, severe escalation of choreiform dyskinesia that had been going on for several hours. His leg movements were so extreme, he had severe bruising from hitting them against the bed rails in the ED. His creatine kinase was more than 21,000 U/L, and his white blood cell count was elevated. Questioning revealed he'd taken extra carbidopa-levodopa. "He had planned on going dancing that night and he didn't want to go 'off'," Dr. Factor said. In the ED, his medications were withheld for 12 hours, and he received intravenous fluids. He was discharged when his creatine kinase was normal, and restarted his drugs.

"People who self-medicate love to be 'on,' even if it increases their dyskinesia," Dr. Factor said. "It's so much better than the alternative for them." Patients may have run out of their drugs, or recently added a new drug that was increased too rapidly or stopped suddenly.

Psychiatric symptoms also cause patients to change their drug regimen, he added, citing the case of a woman with Parkinson's-related psychosis. She'd been prescribed 100 mg/day of quetiapine after a suicide attempt, but the dose was cut to 50 mg several years later. After the drop, "she heard the voice of God telling her to stop her medications, and became severely immobile," Dr. Factor said. Psychiatric symptoms resolved after quetiapine was increased from 50 mg to 400 mg.

Abrupt stop of dopaminergic medications can lead to Parkinson's hyperpyrexia syndrome (PHS). Its clinical features are nearly identical to neuroleptic malignant syndrome: severe rigidity with tremor progressing to immobility. Within 72-96 hours, most patients develop fever (up to 107° F) and altered state of consciousness (from agitation and confusion to stupor and coma), plus autonomic dysregulation (tachycardia, tachypnea, labile blood pressure, urinary incontinence, or diaphoresis). There will always be leukocytosis and elevated creatine kinase. PHS is rare but serious—about 30% don't fully recover, and about 4% die.

PHS is usually tied to abrupt stop of drugs, including drug holidays, noncompliance, unsure diagnosis, or sudden alteration of drug regimen. ■

Tips for Calming Patients' Motor Fluctuations

The primary goal should always be to identify and treat any constitutional illness, said Dr. Stewart Factor. But if no underlying illness is present, drug therapy must be focused on breaking the motor cycle and then tailoring medical therapy to the patient's needs.

"Alteration in Parkinson's medications must be individualized with the goal of trying to maintain a more constant peripheral level of levodopa," he said.

For prolonged "off" periods, consider the following approaches:

- ▶ Use more frequent carbidopa-levodopa (C/L) doses.
- ▶ Make quick-absorb C/L by dissolving tablets in tap water with ascorbic acid and dividing into hourly doses.
- ▶ Try adding a dopamine agonist.
- ▶ Use parenteral injection of apomorphine hydrochloride. "This drug when administered subcutaneously has a rapid onset, usually within 10 minutes, and a short duration of about 1 hour," Dr. Factor said. "It has been used to rescue patients from intractable off periods, consistently improves off periods, and its effectiveness can be maintained for years."
- ▶ Try controlled-release C/L.

For peak-dose choreiform dyskinesias, consider these strategies:

- ▶ Lower the dose of C/L or hold the medication until the symptoms improve.
- ▶ Try a mild sedative (lorazepam, alprazolam, or clonazepam) in the meantime. "This is particularly useful when dyskinesias are worse at night, and can be utilized in the ED while waiting for the dopaminergic medications to wear off," he said.
- ▶ Controlled-release C/L may be a better choice, because its peak plasma level is lower than the standard formulation. This may worsen diphasic dyskinesias, however, especially if given in the evening.
- ▶ Do not give patients any of the typical neuroleptics such as haloperidol or prochlorperazine, because they can ultimately worsen Parkinson's.