Don't Overlook Drug-Induced Parkinsonism

The older, conventional antipsychotic drugs have been most commonly associated with the problem.

BY KERRI WACHTER
Senior Writer

WASHINGTON — The diagnosis of drug-induced parkinsonism often gets missed, even by neurologists, according to an informal study of patients at one movement disorder clinic presented at the World Parkinson Congress.

Of all new patients with parkinsonian symptoms seen in the movement-disorders program at Emory University, Atlanta, between January 2004 and January 2006, 8% (23 of 304 patients) were diagnosed with drug-induced parkinsonism (DIP), said Dr. Stewart A. Factor, director of the program. The age range at diagnosis was 49-97 years; the age at onset ranged between 48 and 96 years. Most patients were female (73%). Records were available for 22 patients with DIP.

"Seventeen of the 22 patients had been seen previously by neurologists, and yet only 2 of them were diagnosed with drug-induced parkinsonism," Dr. Factor said. Of these, 10 were misdiagnosed with Parkinson's disease (PD) and were treated with antiparkinsonian drugs. Seven patients had no clear diagnosis.

With long-term use of the antiemetic drug metoclopramide, patients can develop drug-induced parkinsonism or tardive dyskinesia.

The older, conventional antipsychotic drugs have been most commonly associated with DIP. It has been assumed that the risk of DIP was reduced with the introduction of atypical antipsychotic drugs. However, Dr. Factor's experience has been just the opposite.

Only three patients in his clinic developed DIP in response to typical antipsychotics (haloperidol, trifluoperazine, and amoxapine). In contrast, 12 cases were caused by atypical antipsychotics (3 from risperidone, 6 from olanzapine, 1 from ziprasidone, and 2 from aripiprazole). Five cases were caused by metoclopramide and two were caused by drug combinations (metoclopramide/reserpine, metoclopramide/ziprasidone).

In terms of clinical features, 11 patients had tardive dyskinesia (including 5 with respiratory dyskinesia), 2 had akathisia, 19 had tremor (17 with resting tremor and 6 with asymmetric tremor, alone or in combination), and 3 had akinetic rigidity. Clinically, 11 patients had psychiatric diagnoses—primarily mood disorders (9 patients)—and 6 patients had neurologic diagnoses (dementia, Huntington's chorea, hydrocephalus). Of the 13 patients who stopped the drug and returned for follow-up, 12 had an improvement in symptoms within about 6 months.

DIP has a subacute onset and all of the cardinal features of Parkinson's disease—tremor, rigidity, bradykinesia, and abnormalities of posture, gait, and balance—can be seen. Akinetic rigidity (without tremor) is seen in most patients with DIP.

Drug-use history and tardive dyskinesia appear to be key to the differential diagnosis. Other factors that can help differentiate DIP from PD include subacute onset, bilateral features, more postural tremor than resting tremor, and the presence of other extrapyramidal signs.

Among psychiatric patients, 90% of DIP cases start in the first 3 months of drug use or within 3 months of a dosage increase. The condition may reverse spontaneously, but this is rare. The condition also may be chronic and progressive. Withdrawal of the drug does not lead to immediate improvement of symptoms, which typically take up to 6 months to resolve.

Metoclopramide, an antiemetic drug used mainly for gastrointestinal disorders, has been implicated in DIP. The drug is intended for short-term use (2-8 weeks), but many patients are treated long term with this drug. "With chronic use, they develop drug-induced parkinsonism or tardive dyskinesia," he said.

Up to 25% of psychiatric patients on metoclopramide may have DIP. Women tend to be affected more often than men, particularly older women. Among patients with metoclopramide-induced parkinsonism, up to 70% have tremor, 70% have postural instability, and 40% have tardive dyskinesia. Once the drug is stopped, improvement typically takes 4 months.

The list of other drugs that have been reported as being associated with DIP includes SSRIs, dopamine depleters, bupropion, phenelzine, lithium, valproate, some cardiac drugs (amiodarone, captopril, verapamil, diltiazem, amlodipine, manidipine, methyldopa), and estrogens.

As to risk factors for DIP, women appear to be twice as likely as men to develop the disorder. Age older than 65 is associated with a five times greater risk. Greater drug potency or dose also plays a role. Less frequently described risk factors include prior brain injury, dementia, HIV infection, certain psychiatric disorders (mood disorders in particular), the presence of tardive dyskinesia, and a family history of PD.

"Recognition is the key to proper management because if you recognize that the drug causes it, you stop the drug if you can and the symptoms will reverse in most patients," Dr. Factor said.

Amantadine and anticholinergics are often used to treat symptoms. Other potential treatments include levodopa, electroconvulsive therapy, propranolol, and clozapine. ■

Changes to Tolcapone Labeling Allow Less Liver Monitoring

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

The Food and Drug Administration has approved new labeling that relaxes the liver enzyme monitoring recommendations for tolcapone, an adjunctive treatment for Parkinson's disease, according to the drug's manufacturer.

The new label recommends monitoring serum glutamic-pyruvic transaminase (SGPT/ALT) and serum glutamic-oxaloacetic transaminase (SGOT/AST) at baseline, then very 2-4 weeks for the first 6 months. After that, periodic monitoring is recommended as the prescribing physician deems clinically relevant.

The drug was approved as Tasmar in January 1998 for adjunctive use in patients whose Parkinson's symptoms are not adequately controlled despite being on adequate doses of levodopa/carbidopa, according to the FDA. By October of that year, FDA had received reports of three cases of fatal fulminant liver failure; the agency said many more cases might have gone unreported. The reports prompted a black box warning on the drug label, citing an increased risk for liver failure of up to 100 times above the background population. The warning recommended liver enzyme monitoring every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months, and then every 8 weeks thereafter.

However, based on a data analysis by Valeant Pharmaceuticals International, which makes the drug, FDA has concluded that the risk of liver failure is probably lower than initially estimated. The analysis included more than 40,000 patient-years of prescription data and laboratory test data from more than 3,400 patients who participated in tolcapone clinical trials.

"Recent data suggests that hepatic dysfunction associated with Tasmar is rare and can be addressed with less restrictive monitoring," Dr. C. Warren Olanow, professor and chair of neurology at Mount Sinai School of Medicine, New York, said in a statement on the company's Web site (www.valeant.com). "The new, less restrictive changes in Tasmar's labeling means that doctors can now feel more confident prescribing [the drug] to a broader patient population."

The new label information should show up soon on the drug's packaging, said Dan Springer, a spokesman for Valeant. ■

Selegiline Serves as Effective Adjunct for PD Symptoms

BY KERRI WACHTER
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WASHINGTON — An orally disintegrating formulation of selegiline appears to be a safe and effective adjunct for patients with Parkinson's disease who are experiencing a deterioration of levodopa response, according to data presented in a poster at the World Parkinson Congress.

Selegiline taken in the orally disintegrating form significantly decreased the amount of levodopa nonresponse time, compared with placebo in two phase III, randomized, double-blind trials, reported Dr. William G. Ondo, of the department of neurology at Baylor College of Medicine, Houston.

A selective MAO type-B inhibitor, selegiline is limited by low bioavailability, extensive first-pass hepatic metabolism, and production of amphetamine metabolites. Orally disintegrating tablets dissolve on first contact with saliva and undergo pregastric absorption, minimizing first-pass metabolism and yielding high plasma levels.

Prior to development of an orally disintegrating form of the drug, selegiline—approved for use as an adjunct in treating patients with Parkinson's disease who experience a deterioration in response to levodopa/carbidopa—had been given as a capsule or tablet to be swallowed.

He analyzed data from two trials of orally disintegrating selegiline versus placebo in patients with erosion of efficacy with optimized levodopa therapy. Patients were older than 30 years, had a confirmed diagnosis of Parkinson's disease, had a documented response to levodopa with a dopa-decarboxylase inhibitor, and had at least 3 hours daily when the beneficial effects of levodopa wore off.

Initially, patients in both trials were randomized to placebo or 1.25 mg of orally disintegrating selegiline per day. At week 6, the selegiline dosage was increased to 2.5 mg per day. The mean baseline number of "off" hours was determined using patient recordings for a 24-hour period for 2 days preceding the initial clinic visit. The mean number of "off" hours throughout the trial were also determined using the diaries for the 2 days prior to clinic visits. Six visits were conducted during the 12-week trial.

In the first trial, 98 patients were randomized to selegiline and 50 to placebo; in the second, 94 patients were randomized to selegiline and 48 to placebo.

Combined results from both trials showed that orally disintegrating selegiline significantly decreased total levodopa "off" time at weeks 4-6. The treatment group had 5 hours per day during which efficacy wore off, compared with 6 hours per day for the placebo group (10% vs. 6% reductions from baseline, respectively).

Orally disintegrating selegiline also significantly decreased the percentage of levodopa "off" time at weeks 10-12. The treatment group had 4.5 hours per day during which efficacy wore off, vs. 6 hours per day for the placebo group (about 13% vs. 7% reductions from baseline, respectively).

Orally disintegrating selegiline was generally well tolerated in both trials. ■