Drug Monitor

Calming Restless Legs

Ropinirole, a nonergot-based dopamine agonist, was recently approved by the FDA for treatment of moderate to severe primary restless legs syndrome (RLS). Results from several clinical trials suggest that it significantly improves symptoms, sleep parameters, and quality of life, compared with placebo, and is well tolerated over the long term (up to 52 weeks). In the largest study of the treatment of RLS to date, the Therapy with Ropinirole Efficacy and Tolerability in RLS US (TREAT RLS US) Study Group offers further support of those earlier findings.

Men and women between the ages of 18 and 79 who had been diagnosed with primary RLS were recruited from 47 U.S. medical centers. Patients were included in the study if they had a baseline total score of at least 15 points on the International Restless Legs Scale (IRLS), a history of at least four to seven nights of RLS symptoms in the past month, and documented RLS symptoms for at least four of the seven nights during the screening phase.

In this double-blind study, researchers randomly assigned the 381 enrolled patients to receive either ropinirole or placebo. At the end of 12 weeks, the mean change in IRLS score between the two groups showed that, compared with placebo, once daily ropinirole (0.25 to 4 mg/day) significantly reduced the overall symptoms of RLS. The improvements were consistent and seen as early as day three of the first week, even at low starting doses. Ropinirole was significantly more effective than placebo in reducing sleep disturbance and improving sleep quality and quantity.

Previous studies have suggested that many patients with RLS become anxious and depressed. In the current study, subsets of patients with mild anxiety symptoms and depression showed a statistically significant improvement in these conditions with ropinirole.

Most participants reported that adverse effects were mild or moderate and did not lead to treatment discontinuation. Fewer than 5% of patients reported experiencing such adverse effects as syncope, hypotension, and orthostatic hypotension, which are associated typically with dopaminergic therapies.

Source: *Mayo Clin Proc.* 2006;81:17–27.

Reducing Defibrillator Shocks

How do antiarrhythmic drugs, such as amiodarone and the beta-blocker sotalol, stack up against standard beta-blocker therapy in reducing the shocks of implantable cardioverter defibrillators (ICD)? Despite decades of use, amiodarone never has been compared with beta-blockers in a randomized, controlled study of patients with sustained or inducible ventricular tachycardia or ventricular fibrillation. One randomized, controlled trial found that sotalol reduced ICD shock risk, but another, smaller study found it to be less effective than standard beta-blocker therapy with metoprolol.

In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial, researchers randomly assigned 412 patients from 39 outpatient ICD clinical centers around the world to receive treatment for one year with either standard beta-blocker therapy (metoprolol, carvedilol, or bisoprolol alone), amiodarone plus one of the study beta-blockers, or sotalol alone.

Of the 138 patients assigned to receive standard beta-blocker therapy, 41 (39%) had shocks—as did 26 (24%) of 134 assigned to receive sotalol and 12 (10%) of 140 assigned to receive amiodarone plus a beta-blocker. Treatment with amiodarone plus a beta-blocker prevented shocks better than either standard beta-blocker therapy alone or sotalol alone—though sotalol alone reduced the risk of shock compared with standard beta-blocker therapy alone.

Patients in the standard beta-blocker therapy group were more likely than those in either of the other two groups to have frequent shocks (more than 10 a year), as well as a first shock followed by another within 24 hours. At one year, however, only 5% of patients assigned to receive standard beta-blocker therapy had withdrawn from treatment, compared with 18% of those assigned to receive amiodarone and 24% of those assigned to receive sotalol. In the group assigned to receive amiodarone plus a beta-blocker, there were higher rates of adverse thyroid and pulmonary effects and of symptomatic bradycardia.

When is the best time to administer amiodarone or sotalol? Researchers note that by delaying therapy, the risk of drug-related adverse effects is lower. This needs to be balanced, however, against the painful experience of receiving ICD shocks, which can negatively affect patients' quality of life. In this study, 10% of patients receiving standard beta-blocker therapy alone had their first shocks in multiples (two or more within 24 hours). On the other hand, the researchers point out, most patients in the study did not have any shocks in the year of follow-up.

Source: *JAMA.* 2006;295:165–171.

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Sunitinib: At What Dose Is Toxicity Manageable?

Sunitinib is a novel oral tyrosine kinase inhibitor with antitumor and antiangiogenic activities. In vitro, sunitinib inhibits the growth of cell lines driven by a variety of growth factor receptors and induces apoptosis of human umbilical vein endothelial cells. The multitargeted agent acts against a number of tumor types, such as renal cell carcinoma, colorectal cancer, non-small cell lung cancer, uterine cancer, and melanoma.

On the basis of the promising preclinical antitumor activity in animal models, researchers at the Gustave-Roussy Institute in Villejuif, France sought to determine the recommended dose, tolerability, basic pharmacokinetics, and antitumor effects of sunitinib in patients with advanced solid malignancies.

All participants had histologically proven, advanced, solid malignancies for which no other therapy was possible and an Eastern Cooperative Oncology Group performance status of 2 or less. Treatment cycles were six weeks long, with sunitinib given continuously for four weeks, followed by two weeks with no treatment. Patients received oral dosages of either 50, 75, or 100 to 150 mg/day.

After conducting a phase I dose escalation study of 28 patients, researchers found that, at a dose of 50 mg/day, sunitinib displayed "manageable toxicity." At that dose, the main adverse effects were sore mouth, edema, and thrombocytopenia (which resolved during the off-treatment period in most patients).

At doses over 50 mg/day, patients experienced adverse skin effects, such as skin yellowing. Of the 28 patients receiving this dosage, 18 had various degrees of hair depigmentation, which was reversible when treatment was discontinued. Patients also experienced asthenia, which was fully reversible during the off-treatment period. At dosages of 75 mg/day and higher, patients experienced hypertension and skin toxicity, and tumor responses were often associated with reduced intratumoral vascularization and central tumor necrosis, eventually resulting in organ perforation or fistula.

Overall, sunitinib induced tumor shrinkage and necrosis in 22 assessable patients. Six patients—including one with an imatinib mesylate resistant gastrointestinal stromal tumor—had objective responses: four were prolonged partial responses and two were cases in which tumor necrosis exceeded 90%. In three patients with local or lung metastasis of renal cell carcinoma, the response lasted 28, 36, and 54 weeks, respectively. In one patient, who had a neuroendocrine tumor, the response lasted 21 weeks. Five other patients—who had either renal cell carcinoma, cervical carcinoma, or a neuroendocrine tumor—showed long lasting minor responses and tumor stabilization.

Source: *J Clin Oncol*. 2006;24:25–35.

Redosing Promethazine

Parenteral promethazine is effective as an antiemetic, but it tends to have significant sedative effects at the standard dosage of 25 mg, especially when used with opioid analgesics. Since available antiemetic options are limited, researchers at Anne Arundel Medical Center, Annapolis, MD examined whether lower doses of promethazine could be effective at relieving nausea and vomiting, while reducing the sedative potential.

Researchers assessed adult inpatients with nausea and vomiting from any cause except chemotherapy or pregnancy. Patients were divided into two sample groups, assigned to receive either low dose promethazine IV (6.25 or 12.5 mg) or ondansetron IV 4 mg. Patients were asked to rate their initial symptoms and nausea, vomiting, and sedation on a scale of one to four at one and three hours following administration.

The ratings were not significantly different between the two promethazine dosage groups or between the promethazine groups combined and the ondansetron group. The researchers found that low doses of promethazine IV were as effective as ondansetron 4 mg in reducing nausea and vomiting—and resulted in equivalent patient sedation. While the study was limited, the researchers say the results support the use of promethazine at a lower dose than the currently recommended 25 mg. ●

Source: *Ann Pharmacother*. 2006;40:45–48.