PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Warfarin Use in Patients with Chronic Kidney Disease

In this issue: Warfarin and chronic kidney disease; pregabalin for restless legs syndrome; bevacizumab for glioblastoma and advanced cervical cancer; and FDA actions.

Warfarin and chronic kidney disease

Don't hesitate to treat your chronic kidney disease (CKD) patients with warfarin if they have atrial fibrillation (AF) — it is safe and effective, according to a large observational study in *JAMA*. In more than 24,000 patients who survived an acute myocardial infarction (MI) and had AF, 22% were treated with warfarin at discharge of which 52% had CKD stage 3 or worse (estimated glomerular filtration rate [eGFR] < 60). The composite endpoint included death, readmission due to MI or ischemic stroke, bleeding, or a combination of the above. Compared to no warfarin use, warfarin was associated with a lower risk of the composite outcome for every level of CKD and, in fact, the benefit was higher for those with lower eGFR. The risk of bleeding was not significantly higher in patients treated with warfarin in any CKD stratum with the rate of bleeding actually less in warfarin-treated patients than nontreated patients. The authors conclude that warfarin treatment was associated with a lower 1-year risk for composite outcome of death, MI, and ischemic stroke without a higher risk of bleeding in patients who had an MI and AF, and this association was not related to concurrent CKD (*JAMA* 2014;311:919-928). An editorialist points out that this study was done in Sweden where warfarin management is the best in world, but they still feel that this study "provides the best evidence today that vitamin K antagonists are associated with improved clinical outcomes and no significant risk of bleeding in patients with myocardial infarction and atrial fibrillation with advanced CKD" (*JAMA* 2014; 311:913-915). ■

Pregabalin for restless legs syndrome

Pregabalin (Lyrica) slightly outperformed pramipexole (Mirapex) for the treatment of restless legs syndrome (RLS) in a recent industry-sponsored trial. In a 52-week, randomized, double-blind trial, 719 patients were randomized to pregabalin 300 mg per day, pramipexole 0.25 mg or 0.5 mg per day, or 12 weeks of placebo followed by 40 weeks of randomly assigned active treatment. Over the first 12 weeks, the improvement in a standardized RLS scale was significantly greater among participants receiving pregabalin and the higher dose of pramipexole than those receiving placebo ($P < 0.001$). A drawback of dopaminergic drugs such as pramipexole is the development of iatrogenic worsening of RLS symptoms over time (augmentation), and this was seen significantly less frequently with pregabalin than with higher doses of pramipexole. Suicidal ideation was higher in the pregabalin group. The authors conclude that pregabalin provided significantly improved treatment outcomes as compared to placebo, and augmentation rates were lower with pregabalin than with higher doses of pramipexole for the treatment of RLS (*N Engl J Med* 2014;370:621-631). ■

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Bevacizumab for glioblastoma and advanced cervical cancer

Bevacizumab (Avastin) is Genentech's blockbuster angiogenesis inhibitor that works by slowing the growth of new blood vessels. The drug is used to treat several types of cancer and is used off label to treat macular degeneration. Bevacizumab has mostly been used to treat recurrent and metastatic cancers such as glioblastoma, but more recently has become standard initial therapy for certain solid tumors such as colon and lung cancer. It was briefly approved for the treatment of breast cancer, but that indication was revoked by the FDA in late 2011. Now, bevacizumab is being looked at for initial treatment of glioblastoma, the most common primary malignant brain tumor, and advanced cervical cancer.

Unfortunately, bevacizumab failed to improve survival in patients with newly diagnosed glioblastoma in two new studies. In the first study, 637 patients with glioblastoma were randomized to standard treatment with temozolomide/radiation therapy along with either bevacizumab or placebo starting at week 4. There was no significant difference in the duration of overall survival (15.7 months with drug vs 16.1 months with placebo). Progression-free survival was prolonged with bevacizumab (10.7 vs 7.3 months), but side effects were more common with the drug, including hypertension, thromboemobolic events, intestinal perforation, and neutropenia. Quality-of-life measures and neurocognition also declined more frequently with bevacizumab. In the second similarly designed study, newly diagnosed patients were also treated with temozolomide/radiation and were randomized to bevacizumab or placebo every 2 weeks for 6 weeks, then maintenance doses of temozolomide and bevacizumab or placebo. More than 450 patients were randomized to each group. Median progression-free survival was longer in the bevacizumab group (10.6 months vs 6.2 months) but overall survival did not differ significantly with overall survival for bevacizumab vs placebo, respectively, 72.4% vs 66.3% at 1 year, and 33.0% vs 30.1% at 2 years ($P = 0.24$). More adverse effects were seen in the bevacizumab treatment arm. These studies suggest that the addition of bevacizumab to standard therapy with temozolomide/radiation does not improve survival in patients with glioblastoma but may improve progression-free survival, but with the possibility of higher rates of significant side effects, including neurocognitive decline (*N Engl J Med* 2014;370:699-708, 709-722).

In the same issue of the *New England Journal of Medicine*, a new study showed that bevacizumab is effective for prolonging survival in women with advanced cervical cancer. More than 450 women with previously treated recurrent disease were randomized to chemotherapy with or without bevacizumab until disease progression, the development of unacceptable side effects, or complete response was documented. The bevacizumab-containing combination chemotherapies were associated with increased overall survival (17.0 months vs 13.3 months; hazard ratio, 0.71; 98% confidence interval, 0.54-0.95; $P = 0.004$) as well as a higher response rate. The drug caused more adverse reactions, including hypertension, thromboembolic events, and gastrointestinal fistulas. The authors conclude that addition of bevacizumab to combination chemotherapy in women with advanced cervical cancer improved median overall survival by 3.7 months (*N Engl J Med* 2014;370:734-743). ■

FDA actions

The FDA has approved droxidopa for the treatment of neurogenic orthostatic hypotension in patients with Parkinson's disease, multiple-system atrophy, and pure autonomic failure. The drug was approved under the accelerated approval program, which allows approval for a serious disease if the drug has an effect on intermediate clinical measures. The approval was based on very short-term clinical trials (2 weeks) where subjects reported a decrease in dizziness, lightheadedness, feeling faint, or feeling as if he/she might black out compared to placebo. Durability of symptom improvement beyond 2 weeks has not been demonstrated. Droxidopa is marketed by Chelsea Therapeutics as Northera.

Last year, a meta-analysis of various non-steroidal anti-inflammatory drugs (NSAIDs) showed an increased cardiovascular risk, with high-dose diclofenac and celecoxib conferring the highest risk while ibuprofen was associated with a lower risk. Naproxen was not associated with cardiovascular risk (*Lancet* 2013;382:769-779, doi: 10.1016/s0140-6736(13)60900-9). Now, an FDA advisory panel is suggesting that there are not enough data to allow the makers of naproxen (Naprosyn, Aleve, etc.) to change their labeling based on those data. The advisors are waiting for the results of the PRECISION trial, started in 2006, which is evaluating the safety of celecoxib vs naproxen or ibuprofen in patients at high risk for cardiovascular disease. ■