Drug Monitor

First Drug for Painful Diabetic Neuropathy

For the estimated 62% of diabetics who experience painful peripheral neuropathy, relief may be closer now than ever before. The FDA recently approved duloxetine hydrochloride, the first drug to be indicated specifically for managing this condition. The drug—which is marketed by Eli Lilly and Company (Indianapolis, IN) as Cymbalta—was first approved in August to treat major depression.

In two randomized, placebo-controlled trials involving over 1,000 patients with painful diabetic neuropathy, 58% of those given duloxetine reported a sustained reduction in pain of at least 30%, compared with 34% of the placebo patients. The mechanism of action is unknown.

The most common adverse effects were nausea, dry mouth, constipation, and diarrhea. Some cases of dizziness and hot flashes also were reported.

Source: FDA News Release. September 7, 2004.

Erythromycin and Sudden Cardiac Death

Avoid mixing erythromycin therapy with a cytochrome P-450 3A (CYP3A) inhibitor, say researchers from Vanderbilt University and Nashville VA Medical Center, Nashville, TN. They found an alarming elevation in risk of sudden death from cardiac causes with this combination of drugs in a previously studied cohort of Tennessee Medicaid enrollees.

The cohort included over one million person-years of follow-up and 1,476 sudden deaths from cardiac causes. The researchers reviewed computerized Medicaid pharmacy files to determine patients' use of erythromycin; amoxicillin; and such strong inhibitors of CYP3A as ketoconazole, itraconazole, fluconazole, diltiazem, verapamil, and troleandomycin.

Current erythromycin use doubled the multivariate adjusted rate of sudden cardiac death compared with no use of study antibiotics. The addition of a CYP3A inhibitor raised the rate further to over five times that of patients who took neither a CYP3A inhibitor nor a study antibiotic. By contrast, the risk did not rise significantly among former users of erythromycin, current users of amoxicillin, or former users of CYP3A inhibitors.

Unlike amoxicillin, erythromycin is known to prolong cardiac repolarization and has been associated with torsades de pointes. Since erythromycin is metabolized by CYP3A, the researchers believe that an increase in plasma erythromycin concentrations due to CYP3A inhibition may explain the concurrent effect of the two drugs on cardiac risk. They also note that the calcium channel blockers verapamil and diltiazem, which accounted for nearly all CYP3A inhibitor use in the study, are both CYP3A substrates and erythromycin is likely to increase their plasma concentrations. Calcium channel blocker overdose has been linked to bradycardia, hypotension, and heart block, which can lead to death. ●

Source: *N Engl J Med*. 2004;351:1089–1096.

No Sweet Dreams with Clonazepam

Based on results from a pilot study conducted in six patients, researchers from Tuscaloosa VA Medical Center, Tuscaloosa, AL and several academic institutions across the country are questioning the widespread use of clonazepam for sleep disturbances in patients with posttraumatic stress disorder (PTSD) related to combat experiences. In this single-blind, placebo-controlled, crossover trial, clonazepam therapy resulted in mild to moderate improvements in patients' ability to fall or stay asleep but failed to reduce the frequency or intensity of PTSD-related nightmares. The researchers point to a general lack of data supporting the effectiveness of benzodiazepines in treating PTSD and call for more definitive studies.

Source: *Ann Pharmacother*. 2004;38:1395–1399.