Drug Monitor

Ranolazine May Cause Dyspnea

Ranolazine is the first in a new class of drugs approved by the FDA for the treatment of chronic stable angina. This piperazine derivative decreases the frequency and prolongs the time to onset of angina as well as improves exercise tolerance. In a recent case study, researchers at Duke University Medical Center and Durham VA Medical Center (DVAMC), both in Durham, North Carolina, reported on a 77-year-old man with chronic renal insufficiency who was evaluated for moderate but progressive dyspnea on exertion (DOE) that may have been associated with his use of ranolazine.

The patient presented to the Geriatric Research Education and Clinical Center of the DVAMC to obtain a second opinion regarding his progressive DOE. During the 2 months prior to his visit, the patient had been taking medications (including ranolazine 500 mg/day) for a variety of heart and renal conditions. The ranolazine had been prescribed by a cardiologist for nonrevascularized left anterior descending lesion and the initial symptoms of fatigue.

Although the patient had experienced some mild fatigue in the previous 2 years, his breathing issues clearly were exacerbated during the 2 months preceding his visit to the DVAMC. The patient noted that, prior to having DOE, he was able to walk 2 miles without difficulty. At the time of his visit, however, he was only capable of walking distances less than 100 ft. The patient's pulse oximetry was 95% while he was sitting; it dropped to 88% after he had walked 80 ft, and returned to 95% after sitting again for several minutes.

After tests ruled out cardiac and pulmonary etiologies, the ranolazine was discontinued during hospitalization because of the coincident onset of the patient's symptoms with the initiation of the drug. One month after ranolazine was discontinued, the patient's symptoms resolved. No further interventions or medication changes were made during that time period.

The most commonly reported adverse effects associated with ranolazine are dizziness, constipation, peripheral edema, and cardiac complications. The study authors note that adverse drug effects, in general, may be misinterpreted as symptoms of underlying disorders, underscoring the importance of risk/benefit assessment for individual patients.

The authors believe this is the first published case of ranolazine-related DOE that required discontinuing the drug to resolve symptoms. They recommend additional studies on ranolazine, given its increasing use for the treatment of chronic angina.

Source: *Am J Geriatr Pharmacother.* 2010;8(1):73–76. doi:10.1016/j.amjopharm.2010.01.002.

Dobutamine's Effect on Blood Pressure Measurement

Dobutamine is widely used as a surrogate for exercise during blood pressure measurements, although its effects on arterial pulse transmission and systolic blood pressure (SBP) amplification have not been studied previously. To investigate dobutamine's effects and determine how well cuff pressures represent aortic pressures during dobutamine infusion, researchers from Upstate Medical University, State University of New York, Syracuse; Baltimore Washington Medical Center, Glen Burnie, Maryland; and the Diagnosis and Therapeutic Center (Centre de Diagnostique et de Therapeutique), Paris, France; conducted a study involving 25 patients undergoing coronary angiography to diagnose or evaluate coronary heart disease.

The research team used a cuff oscillometer to simultaneously measure the patients' brachial arterial pressures with directly recorded aortic pressures at rest and during increasing dobutamine infusion rates. Applanated radial pulses were fed into a SphygmoCor device and calibrated in 2 different ways to predict aortic pressures in 15 of those patients.

The researchers found that during dobutamine infusion, the oscillometric cuff SBP regularly overestimated the directly measured aortic SBP, whereas the SphygmoCor-derived aortic SBP underestimated it. At peak dobutamine infusion, amplification of SBP averaged 14.9 mm Hg. The SphygmoCor underestimated the aortic SBP at all dobutamine doses when radial artery pulses were calibrated using cuff pressures. When calibrating radial artery pulses with the more accurate aortic mean and diastolic BPs, however, the SphygmoCor predicted aortic SBP accurately at baseline but not at higher dobutamine doses.

The researchers theorize that the increased pulse amplification during dobutamine infusion was caused by reduced amplitude and changed timing of reflected waves. In most cases, the authors say, the SBP differences would not affect the conduct of routine stress tests to detect coronary heart disease. However, these differences do lead to falsely elevated values

in calculating rate-pressure product and left ventricular wall stress. The study findings support the need for better noninvasive methods to measure aortic pressure.

Source: *Am Heart J.* 2010;159(3):399–405. doi:10.1016/j.ahj.2009.12.010.

Antidepressants in Patients with Diabetes

In a recent secondary analysis, researchers examined aggregate data from published trials conducted at Washington University, St. Louis, Missouri; University of Arizona, Tucson; and University of Washington, Seattle; to identify the rates and predictors of initial response to antidepressant pharmacotherapy in adults with type 2 diabetes.

The researchers studied 387 patients, all of whom received up to 16 weeks of open-label, acute-phase treatment using bupropion (n = 93) or sertraline (n = 294). They used conventional markers for initial treatment outcome (improvement, response, partial remission, and remission) and used logistic regression analysis to identify significant predictors of poor treatment outcome (no improvement, nonresponse, nonpartial remission, and nonfull remission). The candidate predictors included age, sex, race, initial Beck Depression Inventory (iBDI) score, type of treatment received, family history of depression, extant diabetes complications (eDC), and HbA_{1C} level.

Of all the participants, 330 (85%) showed some degree of symptomatic improvement. Additionally, of these patients, 232 (60%) met criteria for response, 207 (54%) met criteria for partial remission, and 179 (46%) met criteria for full remission. Several significant independent predictors of poor outcome appeared: eDC (for no improvement); sertraline treatment, eDC, and higher iBDI (for failure to partially remit); and younger age and higher iBDI (for failure to fully remit). The presence of complications predicted 3 of 4 measures of nonresponse and was the only predictor of treatment resistance, which was defined as no decrease in symptom severity.

Baseline HbA_{1C} levels did not predict depression treatment outcome, as they had in a previous study, the researchers say. They add that poor compliance with blood glucose monitoring has been shown to predict nonremission of major depression with cognitive behavior therapy. The investigating team notes that of patients with diabetes who achieve recovery, one-third experience a recurrence within 1 year and fewer than 10% remain depression-free for 5 years.

The researchers say that their "results indicate that response to depression treatment in type 2 diabetes is influenced by a multidimensional set of factors." They suggest that physical disease markers, initial depression severity, demographics, and other clinical variables are all relevant when treating depression. Auxiliary treatment of pain and impairments could help ensure better outcomes.

Source: *Diabetes Care.* 2010;33(3):485–489. doi:10.2337/dc09-1466.

Errors in Opioid Prescribing

Errors in opioid prescribing for cancer pain are common and complex, according to researchers from The Cleveland Clinic's Taussig Cancer Institute in Ohio. During a survey of prescribing patterns in patients referred to their Palliative Medicine Program, they found that many of the patients had at least 1 incorrect opioid order.

Over a period of 80 days, the researchers screened 238 patients (52 had noncancer diagnoses; 186 had cancer diagnoses). Of the patients with cancer, 117 (63%) had cancer pain. The percentage of cancer pain found in patients who were younger than 65 years was higher than in those aged 65 years and older (62% and 39%, respectively).

The total number of detected opioid prescribing errors was 151, with 82 (70%) patients with cancer pain having had at least 1 incorrect opioid order. Females were more likely to experience multiple errors, although the sex difference did not meet statistical significance. The types of errors varied and encompassed many areas, such as strategy, conversion, rotation, titration, and the use of adjuvant analgesics. The most common opioid prescribing errors were failure to order around-the-clock opioids for constant pain, and failure to treat or prevent opioid adverse effects. Neither pain severity nor reason for consultation had an impact on the errors.

The researchers suggest that the opioid prescribing problem is both systems and operator dependent. For example, they say that failure to order around-the-clock opioids may reflect poor assessment, difficulty in dose titration as initial strategy, underestimation of pain severity, or inadequate knowledge about opioid prescribing and pharmacology. Failure to recognize and appropriately treat different temporal pain patterns (such as constant vs intermittent or incident vs nonincident) also can lead to poor pain management and mislabeling pain as refractory, they add.

Since their patients were referred from multiple specialties, the researchers note that the issue transcends any single specialty. They say that pain management consultations effectively identified and corrected the dosing errors.

Source: *J Pain Symptom Manage.* 2010;39(4):702–711. doi:10.1016/j.painsymman.2009.09.009.

Racial Differences in Androgen-Deprivation Therapy

A recent study found that African American men with metastatic prostate cancer are less likely than white men to receive androgen deprivation therapy (ADT), and when they are treated, they have a longer time to receipt. ADT, which is widely used for the management of symptoms of advanced prostate cancer, also has been shown to slow the progression of the disease.

The study was conducted by researchers from University of Alabama at Birmingham; Meharry Medical College, Nashville, Tennessee; and University of North Carolina at Charlotte, University of North Carolina at Chapel Hill, and The Carolinas Center for Medical Excellence, Cary, all in North Carolina. Their objective was to assess use trends both for ADT overall and by type (orchiectomy and luteinizing hormone-releasing hormone [LHRH] antagonists). They also examined the factors associated with time to receipt for metastatic prostate cancer.

The researchers note that previous studies have found comparable use of ADT by white patients and African American patients, but suggest that those findings may have been the result of the multiple treatment options available for the earlier stages of prostate cancer. In contrast, their study included only metastatic prostate cancer, for which ADT has been the primary therapy for decades.

The data for their study were obtained from the Surveillance, Epidemiology and End Results (SEER) cancer registry—which collects population-based cancer registry data for demographics, tumor site, tumor morphology, stage at diagnosis, and treatment for incident cancer cases from the state or regional SEER cancer registries. These SEER data then are linked to Medicare beneficiary claims data. The researchers looked at 5,273 men, all of whom were aged 65 years and older and were diagnosed with stage IV prostate cancer (during the period of 1991 to 1999). In order to examine the factors that were associated with mean time to receipt of ADT, an accelerated failure time regression model with log-normal distribution was used, while analysis of variance and linear regression were used to assess group differences in ADT use.

Overall, 28% of the participants did not receive any ADT, 29% received an orchiectomy, and 43% received an LHRH agonist. The proportion of participants who did not receive ADT remained relatively stable throughout the period. However, a greater proportion of African American men did not receive ADT compared with white men (38.8% vs 25.5%, respectively; $P < .001$) after diagnosis.

Differences also were observed in the time to receipt of ADT, with African American participants having a longer mean time to receipt of orchiectomy (time ratio = 1.50; 95% confidence interval = 1.03, 2.17) or LHRH agonist (time ratio = 1.42; 95% confidence interval = 1.06, 1.89) than the white participants. The racial difference persisted as the months since diagnosis increased. In addition, when comparing the use of an LHRH agonist vs orchiectomy among men who had received ADT, African American men had a 19% longer mean time to receipt than white men, although this association was not statistically significant.

The researchers say that although the treatment and management of prostate cancer has improved over the past decade, "the disproportionate number of African American men who did not receive ADT for metastatic prostate cancer mirrors the racial differences in the treatment of clinically localized prostate cancer, where African American men disproportionately receive nonaggressive treatment." Because African American men tend to present with more clinically aggressive prostate cancer, the researchers say, it would be expected that they would be treated with ADT more frequently and earlier than white men, but that is not the case, say researchers.

While the racial differences in mean time to receipt were small, the overall range in time to receipt was wide during the study period. They suggest that this could be relevant given the debate about the most appropriate time to administer ADT for metastatic prostate cancer. They also say that further research is warranted to identify and address the factors that contribute to the racial disparities in ADT use and time to therapy receipt for metastatic prostate cancer.

Source: *J Pain Symptom Manage.* 2010;39(5):872–881. doi:10.1016/j.jpainsymman.2009.09.013.