Drug Monitor

Does Rosiglitazone Increase Cardiac Risk?

Patients with type 2 diabetes who take rosiglitazone may have a higher risk—possibly up to 40%—of myocardial infarction (MI) and cardiac death compared with patients taking placebo or other antidiabetic medications. Although the FDA approved rosiglitazone to treat type 2 diabetes in 1999, the agency issued a safety alert this May after the drug's manufacturer, GlaxoSmithKline (London, United Kingdom), reported results of a meta-analysis of 42 randomized, controlled clinical trials. These results, which were published in the June 14 issue of the *New England Journal of Medicine* (NEJM), showed increased cardiac risks in patients receiving short-term (six-month) treatment.

Other data, however, dispute these findings. On June 5, for example, interim results of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia (RECORD) trial, a GlaxoSmithKline-sponsored study, were published online by NEJM. The study authors found no statistically significant differences between the rosiglitazone group and the control group regarding MI and death from cardiovascular or any other causes. These findings are based on data collected over 3.75 years, slightly more than half of the planned study duration.

The FDA will continue to analyze all available data and will review this issue in an advisory committee. The agency also is looking into whether pioglitazone, the other approved "glitazone," has similar cardiovascular risks. Given the inherent risk associated with switching patients with diabetes from one treatment to another, the FDA has not ordered GlaxoSmithKline to take any specific action. Instead, the agency urges health care providers and their patients to discuss treatment decisions.

Sources: FDA news release. May 21, 2007.

N Engl J Med. 2007;356(24):2457–2471. doi: 10.1056/NEJMoa072761.

N Eng J Med. doi:10.1056/NEJMoa073394. [published online ahead of print June 5, 2007.]

GlaxoSmithKline news release. June 6, 2007.

More Morphine May Not Equal Less Pain

Several studies have shown that the generally accepted morphine dose of 0.10 mg/kg given to patients in the emergency department (ED) may be inadequate to control acute, severe pain. But researchers from Albert Einstein College of Medicine, Bronx, NY found that, while boosting the dose to 0.15 mg/kg was safe, it was only marginally more effective.

Of the 280 study patients treated in the ED of Montefiore Medical Center, Bronx, NY, 138 were randomly assigned to receive 0.10 mg/kg of morphine and 142 were randomly assigned to receive 0.15 mg/kg (delivered in two doses). At 60 minutes, 73% of the patients who received the lower dose and 84% of those who received the higher dose reported "good" or better satisfaction with the pain medication.

In terms of actual pain relief, 53% of the higher dose patients reported 50% or greater pain reduction at 60 minutes. In the lower dose group, 44% of patients reported the same. The researchers hypothesized that a 50% increase in analgesia would increase pain relief, albeit at the risk of more adverse events. Surprisingly, however, the additional medication increased neither pain relief nor adverse events.

What could be the reasons behind the lack of greater clinical efficacy with the higher dose? The researchers say it's possible that the maximum potential effect of morphine is exceeded at doses higher than 0.10 mg/kg, although they concede that this idea seems "biologically implausible." A more likely explanation is that some patients may need to receive a threshold amount of morphine before recognizing and reporting a clinically important improvement in pain management. The researchers recommend further investigation into morphine dosing, which they note has lacked systematic evaluation. In the meantime, they recommend individually titrating morphine doses or trying alternate analgesic agents.

Source: *Ann Emerg Med.* 2007;49(4):445–453. doi:10.1016/j.annemergmed.2006.06.030.

Combining COPD Treatments

Which is the more effective method for managing chronic obstructive pulmonary disease (COPD) and maintaining quality of life—nebulizer or inhaler? According to findings from a study funded by Dey Laboratories, Napa, CA (manufacturers of the DuoNeb nebulizer used in the study), the answer may be both.

Conducted by researchers from the David Geffen School of Medicine at the University of California, Los Angeles; Talecris Biotherapeutics, Inc., Triangle Park, NC; University of the Pacific Thomas J. Long School of Pharmacy and Health Sciences, Stockton, CA; and Quintiles Strategic Research Services, San Francisco, CA, the 12-week, multicenter, single-blind study included 140 male and female patients over age 50. Participants were divided into three groups: nebulizer only (single unit dose vial of albuterol plus ipratropium

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four times daily), inhaler only (two puffs four times daily of albuterol and ipratropium), or concomitant treatment (nebulizer in the morning and night, and inhaler in the afternoon and evening). At baseline, and again at six and 12 weeks, the researchers assessed quality of life using the validated, self-administered St. George's Respiratory Questionnaire and conducted spirometry before and after dosing. Patients also recorded six symptoms, including breathlessness and cough, in a daily diary. Of the enrolled patients, 126 completed at least one postbaseline assessment and 97 completed the entire study.

At week six, the nebulizer only and concomitant treatment groups achieved statistically significant improvements from baseline in symptom scores on the questionnaire, and the concomitant group had clinically and statistically significant improvement in total questionnaire scores. All three groups showed little change over time in peak flow or forced expiratory volume in 1 second (FEV_1). Both groups who used the nebulizer, however, had significant improvement ($P = .0196$) over time in diary symptom scores, although differences between groups were not significant.

The researchers state that their study is unique in that previous investigations comparing nebulizer and inhaler were conducted in unnatural settings that do not reflect the way patients actually use the treatments. They acknowledge that their study was limited by a lack of double-blinding—leading to the possibility of patient bias toward nebulizers—and by the self-reporting methods used for several endpoints. They note that, because the three treatments were similar in terms of changes in peak flow, pre- and post-bronchodilator FEV_1, and symptom scores, the main difference was in quality of life. They say the appeal of the combination is that it offers patients additional symptom relief through use of the nebulizer and the convenience of the more portable metered-dose inhaler when the patient is away from home.

Source: *Am J Med.* 2007;120(5):435–441. doi:10.1016/j.amjmed.2006.07.043.

SSRIs for Depression in Heart Failure

Depression is frequently observed in patients with heart failure (HF), adversely affecting quality of life (QOL) and prognosis. But while pharmacologic treatment has been shown to reduce depressive symptoms in patients who've had a myocardial infarction, the effects of antidepressants on patients with HF have not been studied. As such, researchers from the University of Maryland School of Medicine and the Baltimore VA Medical Center, both in Baltimore, MD, evaluated the efficacy of controlled-release (CR) paroxetine, a selective serotonin reuptake inhibitor (SSRI), in treating depression and improving QOL for patients with HF.

The 12-week, double-blind, randomized, placebo-controlled study included 28 patients with chronic HF who exhibited a score of 10 or higher on the Beck Depression Inventory (BDI). Depressive symptoms, clinical status, adverse effects from the medication, and QOL were assessed at baseline and at weeks four, eight, and 12. The paroxetine CR dosage was initiated at 12.5 mg/day and increased to 25 mg/day after two weeks.

Compared with those receiving placebo, significantly more patients treated with paroxetine CR had their BDI scores drop below 10 (69% versus 23%). Regardless of treatment group, reductions in depression were correlated with improvements in psychological but not physical QOL scores. Interestingly, placebo patients who experienced relief from depression reported significantly greater improvements in social functioning compared with paroxetine patients who experienced similar depression relief. This finding, the researchers say, may suggest the importance of social isolation as a factor contributing to depression in patients with HF.

Paroxetine CR was well tolerated, with only one patient reporting lightheadedness after the dose was increased. One patient in the paroxetine group died of HF-related causes after the eight week follow-up.

Since emotional well-being can lead to helpful behaviors, such as adherence to treatment and physical activity, the researchers contend that treating depression is an important component in managing HF. They recommend that larger controlled trials be conducted to confirm the effectiveness of SSRIs and to determine which patient subgroups are most likely to benefit from treatment.

Source: *Am Heart J.* 2007;153(5):868–873. doi: 10.1016/j.ahj.2007.02.024.

A Patch for PD

The FDA has approved the first transdermal patch (Neupro, Schwarz Pharma, Monheim, Germany) to treat the symptoms of early Parkinson disease (PD). The silicone-based patch is replaced every 24 hours and delivers a continuous dose of rotigotine, a dopamine agonist.

The effectiveness of the patch was demonstrated in three randomized, double-blind, placebo-controlled trials that included 1,154 patients with early PD who were taking no other treatments for the disease. Commonly reported adverse effects included skin reactions at the patch site, dizziness, nausea, vomiting, drowsiness, and insomnia, most of which are typical of dopamine agonists. Some patients also reported sudden onset of sleep while engaged in routine activities, hallucinations, and postural hypotension. ●

Source: FDA news release. May 9, 2007.