Drug Monitor

ONLINE EDITION

Does Ivabradine Benefit Diabetic Patients with Stable Angina?

The novel antianginal drug ivabradine, which was approved for use in Europe in 2005 but has not been FDA approved to date, lowers the heart rate through selective inhibition of the heart's I_f current. Previous studies demonstrated the drug's efficacy and safety in managing stable coronary artery disease (CAD) to be comparable to that of the beta-blocker atenolol and the calcium channel blocker amlodipine. But does this hold true specifically for patients with diabetes?

To find out, researchers from State University of New York Downstate Medical Center, Brooklyn, NY and Université de Montréal, Montréal, Canada analyzed data from eight multicenter, randomized, double-blind, controlled trials. Six of the trials enrolled patients with chronic stable angina pectoris and documented CAD, one enrolled patients who had documented CAD and had been treated for congestive heart failure, and one enrolled patients with documented CAD with or without angina. Three studies compared ivabradine to placebo, three compared the drug to atenolol, one compared it to amlodipine, and one compared two ivabradine doses to one another. Collectively, the trials involved 3,079 patients without diabetes (2,372 who received ivabradine, 352 who received atenolol, and 355 who received amlodipine) and 667 with diabetes (535 who received ivabradine, 83 who received atenolol, and 49 who received amlodipine).

The researchers found no obvious differences in the absorption, metabolism, and excretion of ivabradine in patients with or without diabetes. At baseline, the resting heart rate was greater in those with diabetes, but both groups experienced a similar heart rate reduction with ivabradine treatment. Additionally, the antianginal and anti-ischemic efficacy of ivabradine was proportionately similar in both groups, indicating that diabetes does not have a negative effect. Ivabradine treatment also reduced angina attack frequency similarly (by more than half) in both groups, despite the fact that participants with diabetes had a slightly lower frequency at baseline.

Since the numbers of patients who received the comparator drugs were much smaller than the number of those who received ivabradine, the researchers point out, the statistical estimates of differences between the patients with and without DM were less precise for those drugs. Nevertheless, the efficacy results for atenolol and amlodipine were comparable to those found for ivabradine.

The researchers noted no special safety concerns for patients with diabetes taking ivabradine. These patients, for instance, did not have higher rates of sinus bradycardia or visual disturbances—both of which are known to be related to the action of ivabradine. Neither was ivabradine associated with adverse effects on glucose metabolism. Given that beta-blocker therapy can reduce both insulin secretion and sensitivity to insulin and may raise blood glucose and hemoglobin A_{1c} levels, the researchers conclude that "ivabradine represents an attractive alternative to beta-blockers in patients with stable angina and DM."

Source: *Am J Cardiol.* 2010;105(1):29–35. doi:10.1016/j.amjcard.2009.08.642.

When PPI Therapy Cures Chronic Diarrhea, Suspect ZES

Zollinger-Ellison syndrome (ZES), a rare condition caused by a gastrin secreting tumor of duodenopancreatic origin, is notoriously hard to diagnose. But clinicians should suspect this syndrome, say physicians from Saarland University Hospital, Hamburg, Germany, when chronic, unexplained diarrhea is alleviated by proton pump inhibitor (PPI) therapy.

They report the case of a patient who presented for evaluation after three years of chronic, painless diarrhea. During that time, he had passed three to five watery stools a day, resulting in a weight loss of 3 kg. A colonoscopy had been performed at the onset of his symptoms, which revealed no pathology. Thus, he was presumed to have irritable bowel syndrome. At the current evaluation, he reported taking no regular medications and having no family history of endocrinopathy or cancer.

Results of physical examination, lower gastrointestinal endoscopy, and serial biopsies were unremarkable. Upper gastrointestinal endoscopy revealed low-grade esophagitis, diffuse gastritis, and multiple superficial postbulbar ulcers. The gastric pH was lower than 2. Histology indicated *Helicobacter pylori*–negative hyperplastic gastritis. Duodenal biopsies, however, revealed villous atrophy and crypt hyperplasia. His fasting gastrin level was 217 pg/mL (reference value, less than 150 pg/mL).

After the patient started PPI therapy at double the standard dose, his diarrhea ceased completely for the first time in three years. This out-

come, in conjunction with the endoscopic findings, supported a clinical diagnosis of ZES despite ambiguous gastrin levels.

After the PPI was withdrawn, another two serum gastrin measurements yielded normal results (124 and 147 pg/mL), and subsequent secretin simulation tests failed to find excessive gastrin production. Results of endoscopic ultrasound were suggestive of a duodenal wall gastrinoma and showed an isolated liver metastasis. The patient underwent pancreaticoduodenectomy and liver metastasis resection. After radical surgical resection, he remained tumor free during a six-year follow-up.

Clinical diagnosis of ZES is difficult, the authors say, because it presents through signs and symptoms of the most prevalent gastrointestinal disorders, such as gastroesophageal reflux and chronic diarrhea. The latter is often the most prominent symptom, as excessive gastric acid causes high intestinal volume loads and mucosal injury.

PPIs may delay early diagnosis by controlling symptoms and by physiologically increasing gastrin levels. Conversely, however, "clinicians should appreciate that any unexplained chronic diarrhea disappearing under PPI therapy is strongly suggestive for ZES and that an appropriate diagnostic evaluation is warranted in such situations," say researchers.

Source: *Am J Med.* 2009;122(11):e9–e10. doi:10.1016/j.amjmed.2009.06.018.