New Drug Gets Boxed Warning

Liraglutide *from page 1*

achieved HbA_{1c} levels of less than 7%, compared with the exenatide patients (43%) (Lancet 2009;374:39-47).

In all five of the FDA-evaluated studies, pancreatitis occurred more often in patients on liraglutide than in those taking other diabetes medicines, a finding reported with exenatide. The package label will state that liraglutide should be stopped if there is severe abdominal pain with or without nausea and vomiting, and should not be restarted if pancreatitis is confirmed. It should be used with caution in people with a history of pancreatitis, the FDA said in a statement.

The most common side effects observed with liraglutide were headache, nausea, and diarrhea. Other side effects included allergic-like reactions including urticaria.

Last April, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 8-5 that the available cardiovascular safety data on liraglutide were adequate to rule out an unacceptable increase in cardiovascular risk when compared with other diabetes drugs. However, the FDA approval requires the manufacturer to conduct postmarketing cardiovascular safety studies, as is now the case with most glucose-lowering drugs. (The advisory panel was not asked to vote on whether liraglutide should be approved, only about the cardiovascular safety.)

The boxed warning states that liraglutide "causes thyroid C-cell tumors at clinically relevant exposures in rodents," based on two preclinical carcinogenicity studies that linked liraglutide to thyroid tumors in rats and mice, some of them malignant. The risk was significantly increased among the rats that received a liraglutide dose 8 times higher than what humans would receive, according to the FDA statement. "It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be determined by clinical or nonclinical studies," the label states. Novo Nordisk is required to conduct a 5-year epidemiological analysis of a health claims database to evaluate thyroid cancer, other cancers, hypoglycemia, pancreatitis, and allergic reactions.

Novo Nordisk is also required to establish a cancer registry to monitor the rate of medullary thyroid cancer in the United States over the next 15 years. The boxed warning states that liraglutide should not be used in people already at risk for medullary thyroid cancer, such as those who have a family history of it or who have Multiple Endocrine Neoplasia syndrome type 2.

Also included in the approval is a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide and a Communication Plan to help patients and providers understand the potential risks of liraglutide and to ensure that its benefits continue to outweigh the risk of acute pancreatitis and the potential risk of medullary thyroid cancer.

As part of the REMS, the communication plan for health care professionals highlights appropriate patient selection, along with a reminder to promptly evaluate patients who develop symptoms suggestive of pancreatitis. ■

Hyperglycemia Predicts Poor Outcomes in TPN

BY HEIDI SPLETE

Hyperglycemia caused by total parenteral nutrition is significantly associated with increased length of stay, risk of complications, and mortality, according to a study of 276 hospitalized adults.

Furthermore, the best predictors of death and complications in total parenteral nutrition (TPN) patients were blood glucose levels both before and within the first 24 hours of TPN, said Dr. Francisco J. Pasquel of Emory University, Atlanta, and his colleagues.

In this study, the researchers reviewed data from 276 consecutive patients at a single hospital. The average age of the patients was 51 years, and 19% had diabetes before entering the hospital. The patients received TPN for an average of 15 days, and most (65%) were surgical patients (Diabetes Care 2009 Dec. 29 [doi: 10.2337/dc09-1748]).

After the researchers controlled for age, sex, and diabetes history, mortality was significantly associated with a pre-TPN blood glucose level of 121-150 mg/dL, 151-180 mg/dL, or greater than 180 mg/dL. In addition, blood glucose within 24 hours of TPN was a significant predictor of mortality. Compared with patients who did not die, deceased patients had significantly higher blood glucose within 24 hours of TPN (162 mg/dL vs. 139 mg/dL) and during days 2-10 of TPN (161 mg/dL vs. 142 mg/dL).

Patients with blood glucose greater than 180 mg/dL within 24 hours of TPN were more than three times as likely to develop pneumonia and more than twice as likely to develop acute renal failure, compared with patients with blood glucose levels below 120 mg/dL.

In addition, patients with higher blood glucose levels during TPN treatment spent significantly more time in both the ICU and the hospital compared with patients with lower blood glucose levels.

The results suggest that early intervention against hyperglycemia may improve outcomes for TPN patients.

"Our study indicates that blood glucose values prior to and within 24 hours of TPN are better predictors of hospital mortality and complications than the mean blood glucose during the entire duration of TPN," the researchers said. ■

VITALS

Major findings: TPN-induced hyperglycemia is associated with longer hospital stay, more complications, and higher mortality rates.

Data source: A review of 276 adult medical and surgical patients who received TPN at a single hospital.

Disclosures: Co-author Dr. Guillermo Umpierrez has received research support from the American Diabetes Association and the National Institutes of Health. The other researchers had no financial conflicts to disclose.

Occult Coronary Artery Disease Found In Diabetic Retinopathy Patients

BY MICHELE G. SULLIVAN

Up to a quarter of patients with diabetic retinopathy may also have unrecognized stenotic coronary artery disease, putting them at risk for heart attack or sudden cardiovascular death, reported Dr. Takayuki Ohno and colleagues at the University of Tokyo.

The investigators found that 12% of patients attending a retinocoronary clinic had undiagnosed coronary artery disease. Diabetic retinopathy (DR) is present in 3 million Japanese citizens, they said; therefore, 363,000 of these people could have unsuspected heart disease. "These estimates suggest that a large number of patients with DR … would remain without diagnoses until a fatal coronary event," they wrote.

'These estimates suggest that a large number of patients with [diabetic retinopathy] … would remain without diagnoses until a fatal coronary event.'

To test this hypothesis, the researchers opened a diabetic retinocoronary clinic in 2007. Patients with type 2 diabetes and DR who were getting outpatient ophthalmologic care were randomly referred to the clinic. There they were asked to undergo a cardiac screening, which included a cardiovascular history, physical exam, risk factor assessment, resting electrocardiography, and an exercise treadmill test. Patients who tested positive were asked to undergo exercise thallium scintigraphy or a coronary computed tomography scan. Those with abnormal results in this second tier of screening were approached for coronary angiography for further diagnosis.

Over an 18-month period, 286 patients were referred to the clinic; 214 were included in the study. Of these, 59 had nonproliferative DR and 155 had proliferative DR. Most patients (82%) were asymptomatic for cardiac problems; 12 % had previously reported atypical chest discomfort (J. Thorac. Cardiovasc. Surg. 2010;139:92-7).

A normal resting ECG was observed in 159 patients (74%). However, 4 patients (2%) had Q-waves, 39 (18%) had nonspecific ST-T changes, 9 (4%) had right bundle branch block, 2 (1%) had atrial fibrillation, and 1 (0.5%) had second-degree atrioventricular block.

A total of 172 underwent an exercise tolerance test. The results were positive in 50 (29%) and nondiagnostic in 15 (9%). A total of 33 patients underwent exercise thallium scintigraphy, with abnormal results in eight (24%). A coronary CT was performed in 24 patients, 7 of whom (29%) showed atherosclerotic coronary artery disease.

A total of 65 patients had a coronary angiography; 55 of these (26% of the entire cohort of 214) had angiographically confirmed stenotic coronary artery disease (CAD). Compared with patients without confirmed CAD, these patients were older (62 vs. 58 years) and more likely to have Q-wave or ST-T changes on resting ECG (47% vs. 21%, respectively). There were no significant differences in serum creatinine, hemoglobin A_{1c}, or lipid levels. A total of 65 patients had a coronary angiography; 55 of these (26% of the entire cohort of 214) had angiographically confirmed stenotic coronary artery disease (CAD). Compared with patients without confirmed CAD, these patients were older (62 vs. 58 years) and more likely to have Q-wave or ST-T changes on resting ECG (47% vs. 21%, respectively). There were no significant differences in serum creatinine, HbA_{1c}, or lipid levels.

During the clinic's daily coronary conference, CABG was recommended for 17 patients, PCI for 25, and aggressive medical therapy alone for 13. So far, 12 have undergone CABG (including 3 for whom PCI was recommended) and 27 have undergone PCI. Three refused to have any type of coronary revascularization.

During the 288-day follow-up period, all patients have remained alive with no myocardial infarction. But eight (four in each intervention group), all of whom had proliferative DR, did experience the vision-threatening complication of vitreous hemorrhage. "Progression of [diabetic retinopathy] involving vitreous hemorrhage can take place spontaneously in diabetic patients after coronary revascularization with either PCI or CABG," but little about its prevalence is known, the authors noted. ■