Pramlintide Equals Meal Insulin, Curbs Side Effects

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Adding an injection of pramlintide at mealtime to basal insulin therapy worked as well as mealtime rapid-acting insulin to control postprandial glucose levels, but caused less weight gain and hypoglycemia, a study of 112 patients with type 2 diabetes found.

The randomized, open-label, 6-month trial showed that 30% of 56 patients in the pramlintide group and 11% of 56 patients in the rapid-acting insulin group achieved the primary composite end point of a hemoglobin A_{1c} (HbA_{1c}) level of 7% or lower, no increase in body weight, and no severe hypoglycemia. The difference was significant, Dr. Matthew Riddle of the Oregon Health and Science University, Portland, reported at the annual scientific sessions of the American Diabetes Association.

Pramlintide is a synthetic analogue of the hormone amylin, with similar glucoregulatory properties. It is approved as adjunctive therapy for patients with type 1 or type 2 diabetes who use mealtime insulin and have not achieved good glucose control despite optimal insulin therapy, with or without oral medications. It is not approved as an alternative to mealtime insulin, said Dr. Riddle, who is an adviser and consultant for Amylin Pharmaceuticals Inc., which markets pramlintide and funded the study.

A prior study by Dr. Riddle and his associates suggested patients with type 2 diabetes on basal insulin glargine could get good postprandial glucose control and cut HbA_{1c} levels by adding mealtime pramlintide without prandial insulin, and without weight gain (Diabetes Care 2007;30:2794-9).

The current study enrolled adults with type 2 diabetes who had baseline HbA_{1c} levels of 7%-10%, were on any combination of oral diabetes medications (metformin, sulfonylureas, or thiazolidinediones), and who were not taking insulin or had used insulin for no more than 6 months at doses of less than 50 U/day.

Both groups started basal insulin (glargine or detemir) on day 1 and titrated as needed, with a fasting plasma glucose goal of 70-100 mg/dL. The pramlintide group started pramlintide (120 mcg before major meals) on day 1 and could titrate down to 60 mcg if needed because of nausea. The rapid-acting insulin group used basal insulin alone for 4 weeks to decrease the risk of insulin-induced hypoglycemia, then added rapid-acting insulin (5 U with major meals).

By week 24, a baseline average HbA_{1c} level of 8.3% in each group had decreased by 0.9% in the pramlintide group and by 1.1% with rapid-acting insulin. In the pramlintide group, 45% of patients reached an HbA_{1c} level of less than 7%, and 29% reached levels below 6.5%, compared with 55% and 32%, respectively, in the rapid-acting insulin group. The differences were not statistically significant in the intent-to-treat analyses.

After 6 months, patients in the rapid-acting insulin group gained an average of 4.2 kg, compared with 0.3 kg in the pramlintide group. Hypoglycemia was seen in 55% of the pramlintide group and 82% of the rapid-acting insulin group. Nausea affected 21% of pramlintide patients and none in the prandial insulin group. Two patients stopped pramlintide because of nausea.

Dr. Riddle also has been an adviser and consultant and has received research support from Eli Lilly & Co., Novo Nordisk Inc., and Sanofi-Aventis, which also make insulin and oral glucose control agents. ■

Population Screens for Type 2 Do Not Cut Mortality Rates

BY ROBERT FINN
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SAN FRANCISCO — A population-based screening program for type 2 diabetes does not decrease all-cause, cardiovascular, or cancer-related mortality over a 5-year period, according to a large randomized controlled trial presented at the annual scientific sessions of the American Diabetes Association.

Moreover, screened patients offered intensive diabetes treatment did no better in terms of mortality than did screened patients offered routine diabetes treatment, said Dr. Justin Basile Echouffo-Tcheugui of the University of Cambridge (England).

The results call into question the value of large-scale screening for type 2 diabetes and of intensive diabetes management. And they conflict with mathematical models that predicted such screening would result in a 26%-40% reduction in diabetes-specific mortality, he said.

The 79,085 people who participated in the study were patients at 32 primary care practices in England. Using data from medical records, researchers calculated patients' Cambridge Risk Score (CRS), which reflects an individual's risk of developing diabetes. Of the original cohort, 19,881 people with CRS scores above 0.17 were included in the study. According to an earlier study, using a CRS score of 0.17 as a cut-off point results in a 70% sensitivity and a 64% specificity in identifying patients at high risk of type 2 diabetes (Diabetes Care 2002;25:984-8).

In five of the practices, having a total of 4,137 high-risk patients, no further screening was done. These patients constituted the control group. In the remaining 27 practices, patients were offered stepwise screening for type 2 diabetes.

In the first step, they were tested for capillary blood glucose and hemoglobin A_{1c}. Those with suspicious results went to the second step: capillary fasting blood glucose. Those with suspicious results from that test underwent a glucose tolerance test for a definitive diagnosis of diabetes.

In 13 practices, with 7,462 high-risk patients, those with diabetes were offered routine diabetes treatment. In 14 of the practices, with 8,282 high-risk patients, those with diabetes were offered intensive treatment. In all, 78% of the high-risk patients in the routine care and intensive care practices attended the stepwise screening, and 407 received a diagnosis of diabetes. During 104,218 person-years of observation (a mean of 5.5 years of follow-up per patient) there were 743 deaths in the screening practices and 192 deaths in the control practices.

After adjusting for the practice, age, gender, and steroid and antihypertensive drugs, the researchers found no significant differences between patients in screening practices and those in control practices in overall mortality, cardiovascular mortality, or cancer mortality. There were also no significant differences between the intensive care and routine care patients in overall, cardiovascular, or cancer mortality.

There were two positive results in the trial. In screening practices, high-risk patients who agreed to be screened had 27% lower overall mortality than did those in the control practices. Those who were offered but declined screening had an 86% higher overall mortality than did controls. But these positive results are less persuasive than the others because the researchers don't know if there were important differences between patients who chose to be screened and those who chose not to be screened.

In response to a question, Dr. Echouffo-Tcheugui acknowledged that one would not expect many deaths in 5.5 years of follow-up in newly diagnosed diabetics. He said he and his colleagues would continue to follow the patients. Dr. Echouffo-Tcheugui said he had no conflicts of interest related to his presentation. ■

HbA_{1c} Levels May Help Predict Post-Arthroplasty Complications

BY SHERRY BOSCHERT
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SAN FRANCISCO — Complications after total knee or hip arthroplasty in patients with diabetes were significantly more common in those with higher hemoglobin A_{1c} levels, a retrospective study of 119 patients found.

The overall rate of medical and surgical complications was more than 50% in patients with a hemoglobin A_{1c} (HbA_{1c}) level greater than 7%, and less than 40% in those with an HbA_{1c} level below 7%, researchers reported.

American Diabetes Association recommendations set a treatment goal of an HbA_{1c} level below 7%.

"Patients with significantly elevated HbA_{1c} levels should have their glycemic control better optimized prior to undergoing total hip [or knee] arthroplasty, as well as in the perioperative period," Dr. Yossef C. Blum said during a poster session at the annual meeting of the American Academy of Orthopaedic Surgeons.

In a review of inpatient and outpatient charts of total knee or hip arthroplasty performed by a single surgeon at one institution from 2000 to 2007, Dr. Blum, of Montefiore Medical Center, New York, and his associates found 199 patients whose HbA_{1c} level had been measured in the year before surgery or within 3 months after the surgery. Those with conditions other than diabetes that led to an immunosuppressed state, such as HIV or rheumatoid arthritis, were excluded.

Patients did not have to have a diagnosis of diabetes to be included—just an HbA_{1c} measurement—because up to a third of people with diabetes do not have a formal diagnosis, they reported.

In all, 73% of the patients underwent total knee arthroplasty and 27% had total hip arthroplasty. Their mean age was 68 years. The cohort was 76% men, 34% white, 34% black, 23% Hispanic, and 9% other races or ethnicities. Their mean body mass index was 34 kg/m^2, and their mean HbA_{1c} level was 6.6% (range 4.9%-12.3%).

A multivariate analysis looking for associations between HbA_{1c} levels and outcomes within 3 months of the surgery showed that higher HbA_{1c} levels were significantly associated with a higher risk for any complications, and surgical site and wound complications after surgery.

Only four surgical site infections occurred—too few to demonstrate a specific association between HbA_{1c} levels and wound infection—but "it is notable that three of four infections occurred in patients with an HbA_{1c} [level] above 7.5%," Dr. Blum said, adding that although too few complications occurred to show a significant association with HbA_{1c} levels, an association might be seen in a larger study.

The current study found no association between HbA_{1c} level and the risk of non–surgical-site infections, urinary retention, or discharge after surgery to an inpatient facility. Overall, 43% of the patients developed medical or surgical complications.

"Future studies with [more] patients may help determine a cut-off HbA_{1c} level above which total hip [or knee] arthroplasty can be considered too high risk," Dr. Blum said.

A 2003 review by other investigators of 290 diabetes patients who underwent noncardiac surgeries found that those with an HbA_{1C} level above 7% had a statistically significant increased risk for postoperative complications. But there have been few studies to date on the results of total knee arthroplasty in diabetes patients, and even fewer studies on the results of total hip arthroplasty in diabetes patients, he noted.

Some reports suggest a risk of 1%-7% for deep infection in diabetes patients after total knee arthroplasty, and overall wound complication rates of 1%-12%. A 1983 study of outcomes after total hip arthroplasty in diabetes patients reported superficial infections in 10% of the patients and deep infections in 7%. ■