Inhaled Insulin Had Little Effect on Lung Function

BY KATE JOHNSON
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COPENHAGEN — Two-year data on the only approved inhaled-insulin treatment show that it has minimal adverse effects on pulmonary function, according to two new studies supported by Pfizer Inc., which manufactures the product (Exubera).

"It's safe, effective, and easy," said Dr. Jay Skyler, who presented one of the studies at the annual meeting of the European Association for the Study of Diabetes. The findings offer reassuring evidence about possible effects on pulmonary function, which "lots of people have been concerned about," he said in an interview. Two previous short-term studies (12 and 24 weeks) of inhaled insulin in patients with type 1 diabetes showed similar findings, but a longer-term study was needed, he added.

Dr. Skyler's study involved 580 patients with type 1 diabetes who were 18-65 years of age and had normal lung function. All were treated with basal insulin and were randomized either to subcutaneous prandial insulin (290 patients) or to inhaled prandial insulin (290 patients) three times daily for 2 years. The primary end point of the study was pulmonary function; secondary end points included blood sugar levels (HbA_{1c}), fasting plasma glucose (FPG), hypoglycemia, and body weight.

The data showed slightly decreased pulmonary function (less than 2% of baseline values) in subjects using inhaled insulin, compared with subcutaneous insulin. "The changes were small, occurred early [by 3 months], and did not progress," said Dr. Skyler, who is a professor in the division of endocrinology, diabetes, and metabolism at the University of Miami.

The incidence of cough was more common in people using inhaled therapy (38% vs. 13%); however, it was predominantly a mild cough that was rarely productive and rarely occurred at night. "Other studies have shown this small change in pulmonary function reverses when the medication is stopped. We are stopping the medication now and then plan to resume it 6 months later to demonstrate this," said Dr. Skyler.

HbA_{1c} levels were maintained in both groups throughout the study, but FPG levels were improved in the inhaled-insulin group, compared with the subcutaneous insulin group (from 170.1 to 156.8 mg/dL, compared with 166.9 to 173.5 mg/dL). The overall rate of hypoglycemic events was similar in both groups; however, there were fewer severe hypoglycemic events in patients using inhaled insulin (2.8 vs. 4.1 events per 100 subject-months, relative risk 0.67). In addition, patients using inhaled insulin experienced less weight gain than did patients using subcutaneous therapy (0.7 kg vs. 2.0 kg), he reported.

A striking difference between the two groups was the level of insulin antibodies, which was markedly elevated in the inhaled-insulin group, said Dr. Skyler. "Antibodies occur in response to any peptide that's given, and there is a greater proclivity to form antibodies anytime something is given across a mucosal surface. What's interesting in this study is that the antibodies went up, and started going down after a year."

He said the issue is not whether antibodies form, but the fact that they had no adverse effect. "They don't impair the action of the insulin in any way or lead to any other adverse effect, and that's consistent with what we know about injected insulin as well."

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Patients who used inhaled insulin had slight decreases in pulmonary function that occurred early and did not progress. Cough was reported by 38%.

In addition to being the principal investigator for Pfizer on this study, Dr. Skyler has chaired Pfizer's global Exubera advisory board and has also worked with all the other companies that are developing inhaled insulin: Novo Nordisk Inc., MannKind Corp., Eli Lilly and Co., and Kos Pharmaceuticals Inc.

A second Pfizer study presented as a poster was designed identically but included 635 patients with type 2 diabetes, rather than type 1 disease. A total of 319 subjects were randomized to the inhaled-insulin arm, whereas 316 received subcutaneous therapy, reported Dr. William Cefalu, professor and chief of the division of nutrition and chronic diseases at the Pennington Biomedical Research Center in Baton Rouge, La., and colleagues. The center is affiliated with Louisiana State University.

For the same primary and secondary end points, the study's results were similar to those of the Miami study, except that all hypoglycemic events, including severe events, were comparable in both groups.

"These data support previous findings that Exubera is an appropriate treatment for adult patients with [type 2 diabetes]. Availability of Exubera may provide an opportunity to increase the acceptance of insulin therapy, and thus improve glycemic control" in patients with type 2 diabetes who are suboptimally controlled on oral agents, wrote the authors.

Dr. Cefalu has served as research investigator for several inhaled-insulin studies for Pfizer and on Pfizer's inhaled-insulin advisory boards. He has worked with all other companies developing inhaled insulin. ■

Inhaled Insulin Less Effective in Diabetics With Lung Ailments

BY KATE JOHNSON
Montreal Bureau

COPENHAGEN — Inhaled insulin is less effective in diabetic patients with chronic lung conditions such as asthma and chronic obstructive pulmonary disease, compared with patients who have healthy lungs, according to data from two industry-sponsored studies presented at the annual meeting of the European Association for the Study of Diabetes.

However, in patients with mild asthma, predosing with a bronchodilator can result in inhaled insulin exposures similar to those for patients without asthma.

The asthma study was supported by Pfizer, manufacturer of the only approved inhaled insulin treatment, Exubera. Eli Lilly & Co. supported the other study.

Exubera is not approved for use in diabetic patients with asthma or chronic obstructive pulmonary disease (COPD), said Robert J. Fountaine, Pharm.D., of Pfizer's department of global research and development, who presented the Exubera study. Studies are under way to support long-term safety and efficacy in those patients.

Dr. Fountaine's open-label crossover study included 67 nondiabetic subjects with asthma: 30 with moderate asthma (those with a mean unmedicated forced expiratory volume [FEV_1] of between 50% and 80% of predicted values); and 37 with mild asthma (defined as between 80% and 100% of predicted values). Also included were 19 healthy, nonasthmatic subjects.

All nonasthmatic subjects received inhaled insulin (3 mg) alone on days 1 and 3, whereas the asthmatic subjects received one of the following regimens in a randomized sequence on days 1, 3, 5, and 7: inhaled insulin alone, 180 mcg of the bronchodilator albuterol (a short-acting β-agonist) followed by inhaled insulin 30 minutes later, albuterol followed by inhaled insulin 10 minutes later, or the inhaled corticosteroid fluticasone (440 mcg) followed by inhaled insulin 30 minutes later.

Investigators collected blood samples at set times, beginning 30 minutes before insulin dosing until 360 minutes after, from which serum insulin and C-peptide levels were calculated. They also performed spirometry before and 10 minutes after each inhaled insulin dose, and before and 30 minutes after each albuterol dose.

The results showed that in the absence of albuterol, pulmonary absorption of inhaled insulin was reduced in patients with mild to moderate asthma, compared with nonasthmatic patients, said Dr. Fountaine. However, prior dosing with albuterol 30 minutes before insulin inhalation increased insulin absorption by 25%-35% in patients with mild asthma (resulting in absorption rates that approximated those in healthy subjects) and by 45%-50% in those with moderate asthma (resulting in absorption rates that were still lower than those seen in nonasthmatic subjects). The administration of fluticasone before inhaled insulin did not adversely affect insulin pharmacokinetics, and spirometry testing showed that inhaled insulin did not interfere with the efficacy of albuterol, he said.

The Lilly-sponsored study evaluated the company's inhaled insulin system, AIR, which is still under development. It found a reduced metabolic effect of inhaled insulin in nondiabetic patients with COPD, compared with healthy patients and compared with subcutaneous insulin administration, said Dr. Klaus Rave of Profil Institut für Stoffwechselforschung in Neuss, Germany.

The study included 15 subjects with healthy lungs and 27 with COPD, of whom 13 had chronic bronchitis and 14 had emphysema. All received two separate doses of inhaled insulin (5.2 mg each) and one dose of subcutaneous insulin (12 U). A euglycemic glucose clamp was used to assess glucodynamic responses, and serum insulin measurements were used to assess pharmacokinetics. Pulmonary function tests and spirometry were also performed.

The results showed that although total insulin exposure and metabolic effect was similar in all subjects after subcutaneous insulin, it was reduced after inhaled insulin in patients with COPD. Insulin exposure after inhaled insulin was cut by 22% in those with emphysema and by 44% in those with chronic bronchitis, compared with healthy subjects. The metabolic effect of inhaled insulin was reduced by 33% in those with emphysema and by 40% in those with chronic bronchitis.

There was no difference in pulmonary function tests done before and after inhaled insulin, but spirometry results showed an FEV_1 decline after inhaled insulin and insulin administered subcutaneously, warranting a long-term safety evaluation of inhaled insulin in COPD patients. ■