Inhaled Insulin—A New Development in Glycemic Control for Patients with Diabetes

a report by
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In January of 2006 the US Food and Drug Administration (FDA) approved the first inhaled human insulin preparation and delivery system, Exubera®. Although many alternate routes of insulin delivery have been studied over the past years, this is the first non-injectable insulin system to become a reality.

Other inhaled insulin delivery systems are in various stages of development and could be available in the next two to three years. Inhaled insulin offers a new and unique approach to insulin delivery. Its availability gives physicians a potent new approach to help patients gain improved glucose control.

Insulin therapy for diabetes was first introduced 80 years ago and changed forever our approach to treatment of this disease. Lifesaving for patients with type 1 diabetes, insulin therapy also plays a major role in the treatment of type 2 diabetes. Studies such as the Diabetes Control and Complications Trial and the United Kingdom Prospective Study have shown that glucose control is key to the prevention of microvascular complications and also may play a large role in the development of macrovascular complications.

Recent guidelines from the American Diabetes Association suggested that the goal for HbA_{1c} should be 6% or less if it can be obtained without significant sides effects. Although glucose control certainly improved since Best and Banting introduced insulin, a recent NHanes III report indicated that we are still far from meeting goals for glucose control in the majority of patients.

Insulin remains the ultimate therapy for patients with diabetes, but a number of barriers prevent optimal use. One of the major barriers is fear of injections by the patient. Other barriers include a wide range of patient misconceptions about insulin, such as risk of side effects and weight gain. Physicians may have similar concerns about weight gain and hypoglycemia.

The challenges of starting a patient on insulin in their office may also play a role. Such concerns by the patient and the physicians often lead to delay in starting patients with type 2 diabetes on insulin or from intensifying a regimen for patients with type 1 diabetes. The availability of inhaled insulin delivery system provides an acceptable means of delivery of insulin to break down some of these barriers.

Since the discovery of insulin over 80 years ago, investigators have sought to develop other routes of insulin injection. The lung has long been considered a target for drug delivery and is the focus of the delivery of a number of medications. The lung has a large surface area for drug absorption, ranging 100–195m^2. In addition, the alveolar epithelium has permeability that allows for rapid absorption of solutes such as insulin.

One important question in the development of inhaled insulin is the form of insulin. The Exubera insulin delivery system employs a dry particle powder formulation, whereas other delivery systems are looking at liquid aerosol formulations.

The basic development of the Exubera insulin and insulin delivery system rested on assessment of the pharmacokinetics and pharmacodynamics of the dry powder insulin delivered to the lung.

A number of studies were done comparing the time action profiles of one time inhalations of Exubera, to regular human insulin and insulin lispro in non-diabetic healthy volunteers, individuals with type 1 diabetes and individuals with type 2 diabetes. In non-diabetic patients Exubera demonstrated a significantly more rapid mean time to maximal concentration than did subcutaneous (SC) insulin.

In these studies the relative bioavailability of Exubera was approximately 10% of the SC insulin in these studies Intra-subject variability was studied in type 2 diabetes and was insignificant.

Comparisons to SC regular insulin and SC lispro injections in non-diabetic patients shown that

Exubera had a more rapid onset of action than regular insulin or lispro, but with a longer duration of action than lispro.

Clinical Studies

The efficacy and safety of Exubera has been assessed in a number of clinical studies in patients with type 1 and type 2 diabetes. Several initial three-month trials were carried out to establish proof of concept and then a number of six-month registration trials were done. In addition data is available from two-year safety trials. In total, over 2,500 patients have been exposed to Exubera.

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Two 24-week open-label, randomized multicenter studies compared the preprandial administration of Exubera in combination with long-acting SC insulin with standard basal-bolus insulin regimens in patients with type 1 diabetes. In one study patients with type 1 diabetes were randomly assigned to receive treatment with either Exubera plus bedtime ultralente SC or two or three injections of SC regular insulin before meals. HbAlc change was similar in both groups at 24 weeks.

A second major 24-week study in type 1 patients compared preprandial Exubera plus morning and evening SC injections of NPH insulin or preprandial regular SC insulin plus morning and evening NPH. As in the previous study, mean decrease in HbA_{1c} at week 24 was comparable for both treatment groups. Both studies were important in showing non-inferiority of treatment with preprandial inhaled insulin versus prepandial regular insulin.

A number of clinical studies have also demonstrated that Exubera provides effective glycemic control inpatients with type 2 diabetes. An initial 12-week study of patients treated with standard SC insulin regimens showed HbA_{1c} reduction when pre-meal SC regular insulin was replaced by inhaled insulin. A 24-week study of pre-meal Exubera and ultralente insulin versus a conventional SC insulin regimen that included regular and NPH insulin was conducted. Comparable decrease in HbA_{1c} was seen in both groups.

Studies with Exubera were conducted in patients who were not well controlled on combination of two oral agents, metformin and various sulfonylureas. Patients were randomized to Exubera pre-meal or to continue on their pre-study therapy for 12 weeks. Mean HbA_{1c} fell by 2.3% in the group receiving Exubera, compared with 0.1% in patients on oral agents only. Patients who were poorly controlled with two oral agents were further studied with a 12-week trial, where patients were randomized either to addition of preprandial Exubera to their oral agent regimen, or prepandial Exubera alone or oral combination alone. Significant HbA_{1c} decrease of 1.9% was seen in the first group, 1.4% decrease in the second group, and 0.2% in the third group. The third interesting study done with patients unable to achieve glycemic control (HbA_{1c} >8%) on diet and exercise alone were treated for 12 weeks with either premeal Exubera or rosiglitasone. Both treatments lowered HbA_{1c}; however, Exubera patients dropped by 2.1% and patients treated with rosiglitazone dropped by 1.4%.

Safety

Overall, Exubera has been proved to be safe and well tolerated. One major concern with any insulin preparation is risk of hypoglycemia. In the two 24-week studies done in patients with type 1 diabetes, the incidence of hypoglycemia was no different to that in treatment groups.

In patients with type 2 diabetes treated with insulin, the incidence of hypoglycemia was also comparable in pre-meal Exubera treated groups verses pre-meal SC treated groups. Overall, rate of events was much lower in the patients with type 2 diabetes than in patients with type 1 diabetes. Rates of hypoglycemia were higher in the Exubera-treated patients on oral agents than in the comparator non-insulin treated groups. Since HbA_{1c} improved substantially in the

Exubera-treated groups on oral agents the higher incidence of hypoglycemia was not unexpected.

Pulmonary Function

One of the major concerns in the development and use of inhaled insulin was pulmonary safety. Mild to moderate cough has been reported in approximately 21%–31% of patients receiving Exubera. The incidence and prevalence of cough generally deceased over time and very few patients, less than 1% discontinued treatment due to cough.

Patients were followed closely for the duration of the studies with repeated pulmonary function testing and chest X-ays. At the end of the 24-week studies, small decreases in FEV_1, and DL_{CO} were noted in the Exubera-treated groups. The changes occurred early in treatment and remained unchanged through the studies. Two-year safety studies were instituted in both patients in type l and type 2 diabetes. The results of those studies were recently reported. Small initial changes occurred, but then remained unchanged, with subsequent parallel mild decline in lung function in both the Exubera-treated patients and the SC treated patients. Exubera was stopped at the end of two years, and the small difference in function resolved.

At this time it is unclear how well Exubera works in patients with various pulmonary diseases and problems, as such patients were not included in the studies. Smoking can affect rate of absorption of Exubera by the alveoli and therefore its use by individuals who smoke is not recommended at this time.

Reports from early studies on Exubera indicated that increased levels of insulin antibodies were seen in Exubera-treated patients versus those patient treated with SC insulin alone. The antibodies were structurally identical to those seen in response to SC insulin administration (mainly IgG). Of importance, is that there was no relationship between insulin antibody concentrations and HBA_{1c} levels, fasting plasma glucose and postprandial glucose, and the incidence of hypoglycemia. Also, there was no relationship between the incidence of allergic and or respiratory adverse events and the antibody levels.

Patient Acceptance

Patient report excellent satisfaction with with Exubera. When Study patients asked as to preference for inhaled versus SC insulin, the greater majority picked the inhaled insulin over SC insulin. Quality of life measures have also been positive in patients taking the inhaled insulin.

Patient Use

Exubera is available in 1mg and 3mg dry blister packets. One mg of Exubera equals three units of regular insulin and 3mgs equals approximately eight units of regular insulin. If a patient wished to take equivalent inhaled insulin to 24 units of regular insulin they would take three separate inhalations of the 3mg dose. An inhalation should be taken approximately 10 minutes prior to the meal. The FDA has mandated that patients have a FEV_1 done at baseline and repeated at six months. A FEV_1 of at least 70% is required for using Exubera. If after treatment the FEV_1 drops by 20% the patient should be withdrawn from inhaled insulin.

Reducing some of the barriers to insulin therapy could improve clinical outcomes and quality of life in patients with diabetes.

Conclusion

Exubera, the first inhaled insulin delivery system, has been approved for patient use and is currently available in the US. It is the first alternate delivery method of insulin which has been shown to be effective and also has long-term safety data. Reducing some of the barriers to insulin therapy could improve clinical outcomes and quality of life in patients with diabetes. Other inhaled insulin delivery systems are also in development. Some of these devices and insulins are now in phase III trials in patients with type l diabetes and patients with type 2 diabetes. ■

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchendocrinedisease.com).