Inhaled Insulin: Safety and Appropriate Uses

From a biological perspective, there are many advantages to inhaled insulin: the lung has a large surface area and a thin blood barrier, inhaled administration avoids first pass liver clearance, and transport of the medication is rapid and efficient. From a quality of life perspective, perhaps the biggest advantage of inhaled insulin is its mode of delivery. Exubera®, an inhaled human insulin co-developed by Pfizer and Aventis, has been FDA approved and became available to patients in the US in July 2006. Exubera® was granted marketing authorization by the EU Commission in January 2006. In addition, six other pharmaceutical companies have inhaled insulin products in development. As these products represent a completely new insulin delivery mechanism, there is obviously a great deal of interest in their effectiveness, safety, and introduction to the marketplace.

The pharmacokinetics of inhaled insulin differ from injected insulin. Serum insulin levels peak more quickly with inhaled insulin compared to regular human insulin administered subcutaneously (49 minutes vs. 105 minutes, respectively). In terms of pharmacodynamics, the duration of glucose-lowering activity of inhaled insulin is comparable to regular human insulin. The within-subject variability of inhaled insulin is comparable to that of regular human insulin. These findings appear to be consistent in patients with either type 1 or type 2 diabetes.

Joseph Brain, ScD of Harvard University gave an overview of inhaled insulin and the associated pulmonary safety issues. There are several reasons that clinicians need to choose carefully which patients are candidates for inhaled insulin. Obesity adversely affects lung volume and respiratory function and increases the risk of asthma and abnormal pulmonary function. Pulmonary microcirculation is also adversely affected by poor glycemic control.

In rats and monkeys treated with inhaled insulin, no pathologic respiratory or significant immunologic changes were observed. However, the doses that could be used were limited because extremely high doses led to hypoglycemia.

Highlights from the
American Diabetes Association Annual Meeting 2006

Studies comparing the effects of inhaled insulin and oral agents on pulmonary function in humans have not shown evidence of airway sensitization, and no acute adverse effects occurred after insulin was inhaled. There was a small decrease in forced expiratory volume at one second (FEV_1) and carbon monoxide diffusing capacity (DL_{co}). These decreases occurred in the first few weeks of treatment, did not progress, and returned to baseline values after inhaled insulin was discontinued. Because of these concerns, patients need to have a spirometric pulmonary assessment and cannot take inhaled insulin if their lung function is <70% of expected (per the Exubera® label). Slight increases in dyspnea and mild cough are common side effects reported in using Exubera®. Dr. Brain advocated the conduct of long term post-marketing studies 5-10 years in length, as the data collected at this point go out only to 2 years.

During its development, inhaled insulin has been used in several different studies in both type 1 and type 2 diabetes. In two 24-week studies conducted in patients with type 1 diabetes, the decrease in HbA1c and number of episodes of hypoglycemia were comparable between inhaled insulin and regular insulin. A summary of the clinical data is presented in the table below.

	Study A		Study B	
Type 1 Diabetes	INH (TID) + UL (QD)	SC R (BID) +NPH (BID)	INH (TID) + NPH (BID)	SC R (TID) + NPH (BID)
Measure	N=136	N=132	N=103	N=103
Baseline HbA1c (%)	7.9	8.0	7.8	7.8
Adjusted mean change from baseline (%)	-0.2	-0.4	-0.3	-0.2
Patients with end-of-study HbA1c < 8% (ADA goal at time of study conduct)	64%	68.2%	74.8%	66.0%
Patients with end-of-study HbA1c < 7%	16.9%	19.7%	28.2%	30.1%
Fasting plasma glucose (mg/dL)	191	198	178	191
Adjusted mean change from baseline (mg/dL)	-32	-6	-23	+13
Mean body weight (kg)	77.4	76.4	76.0	76.9
Adjusted mean change from baseline (kg)	0.4	1.1	0.4	0.6

INH = Exubera® inhaled insulin
UL = Humulin® U Ultralente®
SC R = regular human insulin
NPH = human insulin isophane suspension
Exubera® package insert, version 2006-01-27

In patients with type 2 diabetes, one open-label study explored the use of inhaled insulin both as monotherapy and as an adjunct to oral antidiabetic (OA) therapy in patients who were not well-controlled using OAs alone. Patients were randomized to one of three arms and were treated for 12 weeks. The incidence of hypoglycemia was slightly higher in the two inhaled insulin groups when compared to the OAs alone. Other results are presented in the following table.

Type 2	INH Monotherapy (pre-meal TID)	OAs	INH (pre-meal TID) + OAs
Measure	N=102	N=96	N=100
Baseline HbA1c (%)	9.3	9.3	9.2
Adjusted mean change from baseline (%)	-1.4	-0.2	-1.9
Patients with end-of-study HbA1c < 8% (ADA goal at time of study conduct)	55.9%	18.8%	86.0%
Patients with end-of-study HbA1c < 7%	16.7%	1.0%	32.0%
Fasting plasma glucose (mg/dL)	203	203	195
Adjusted mean change from baseline (mg/dL)	-23	+1	-53(p<0.0001 vs. OAs alone)
Mean body weight (kg)	89.5	88.0	88.6
Adjusted mean change from baseline (kg)	2.8	0.0	2.7

INH = Exubera® inhaled insulin
OAs = insulin secretagogue + metformin or thiazolidinedione
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Julio Rosenstock, MD of the Southwestern Medical Center gave advice on selecting the appropriate patients for inhaled insulin therapy. In his experience, patients seem to find it easy to use and like using it, but it is contraindicated in patients who smoke, have underlying lung disease, are pregnant, and in pediatric patients. In type 1 diabetes, it should be used in combination with long-acting insulin. In type 2 diabetes, it could be used as monotherapy or in combination with long-acting insulin. He believes that inhaled insulin represents another option for stable patients with type 1 diabetes, and has great potential in type 2 diabetic patients.