

Continuing Education for Pharmacists

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A New Era in the Management of Diabetes: Inhaled Insulin

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Goals. The goal of this lesson is to discuss the use of inhaled insulin in management of type 1 and type 2 diabetes mellitus.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. describe key points relative to diabetes, and patient reactions to the use of injectable versus inhaled insulin;
2. identify physical and chemical characteristics that define the overall action of inhaled insulin;
3. explain the physiologic and pharmacologic principles that define

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the therapeutic usefulness of inhaled insulin; and

4. select, from a list, important points to pass along to patients relative to correct use of inhaled insulin.

FDA has approved the first-ever inhaled insulin (Exubera), which is a new alternative to injectable insulin for the more than five million Americans who use insulin. Exubera is the first new insulin delivery option introduced since insulin was first used more than 80 years ago. It is a powder form of recombinant (rDNA) human insulin for the treatment of adult patients with type 1 and type 2 diabetes mellitus (Table 1).

Background on Insulin

The therapeutic insulin era began January 11, 1922, with the first clinical use of insulin following its discovery by Banting and Best. In the ensuing 80 years, scientists discovered the basic pathophysiology of diabetes, elucidated insulin's structure, and directed their attention to developing improved insulin formulations (e.g., NPH, Lente). These advancements led to development and availability of rapid-acting (e.g., aspart, glulisine, lispro) and basal insulin (e.g., glargine) analogs, which have resulted in routine

Table 1
Diabetes Facts

- 20.8 million people in the U.S. (7 percent of the population) have diabetes.
- An estimated 14.6 million people (of the 20.8 million) have been diagnosed with diabetes; unfortunately, 6.2 million (nearly one-third of the total) are unaware they have the disease.
- There are 41 million Americans with pre-diabetes, in addition to the 20.8 million.
- To differentiate between pre-diabetes and diabetes, a Fasting Plasma Glucose Test (FPG) or an Oral Glucose Tolerance Test (OGTT) can be done. The American Diabetes Association recommends the FPG because it is easier, faster, and less expensive to perform.
- With an FPG test, a fasting blood glucose value between 100 and 125 mg/dL signals pre-diabetes. A level of 126 mg/dL or higher defines diabetes.
- For the OGTT test, if the 2-hour blood glucose level is between 140-199 mg/dL, the person is pre-diabetic. A value of 200 mg/dL or higher means the person tested has diabetes.
- Persons with pre-diabetes do not automatically progress to diabetes. Those who lose weight and increase their physical exercise can often prevent or delay the disease.
- Among adults with diagnosed diabetes, 16 percent take insulin only, 12 percent take both insulin and oral hypoglycemics, 57 percent take oral hypoglycemics only, and 15 percent take neither insulin nor oral hypoglycemics.

use of insulin regimens that closely approach physiological conditions.

Because insulin is essential in controlling type 1 diabetes, a

noninvasive delivery system is a more convenient alternative. The progressive decline in beta-cell function that is the hallmark in pathogenesis of type 2 diabetes means that many patients will eventually fail on oral antidiabetic therapy and require insulin at some point.

Numerous long-term prospective clinical trials have demonstrated the benefits of tight glycemic control in reducing the risk of secondary complications in persons with type 1 and type 2 diabetes. Other studies have shown that despite the benefits of tight glycemic control, which ultimately may only be achieved with insulin in type 2 diabetic patients, there is reluctance on the part of many patients, and oftentimes their physicians, to initiate insulin therapy. This reluctance may be due to the social stigma of diabetes, lifestyle restriction, sense of guilt or failure, weight gain, perception of worsening pathology, physical limitations to drawing up insulin, or needle anxiety. Physicians, therefore, often prescribe a simple regimen initially in order to assure maximum patient compliance.

It should be stressed that many individuals with type 2 diabetes have a positive regard for injectable insulin in terms of efficacy, prevention of complications, and improved overall health. For various reasons, insulin use may be reserved as a last resort for therapy after the stepwise approach of diet, exercise, and oral antidiabetic agents have failed to produce and maintain adequate glycemic control. However, *many* (some reports say *most*) patients eventually require exogenous insulin to attain glycemic control targets.

Diabetes: The Disease

Despite therapeutic advances, the incidence of both type 1 and type 2 diabetes continues to increase in the U.S. with type 2 at epidemic proportions. Type 1 disease typically develops when the body's immune system destroys the pancreatic beta

cells. Risk factors may be autoimmune, genetic, or environmental. There is presently no way to prevent type 1 diabetes.

Type 2 diabetes is associated with decreased sensitivity to insulin in muscle, liver, and adipose (i.e., fat) cells, as well as progressive decline in pancreatic insulin production. The precise causes of insulin resistance with eventual beta-cell failure remain unclear; however, it appears that both genetic predisposition and environmental factors interact. Obesity and sedentary lifestyle are closely linked to both onset and progression of type 2 diabetes; weight loss, exercise, and selective medications can often delay or prevent its onset.

The leading cause of morbidity and mortality in patients with diabetes is cardiovascular disease. A marker of insulin resistance, hyperinsulinemia, is an independent risk factor for cardiovascular disease. Diabetes treatments that decrease hyperinsulinemia and/or insulin resistance seem to protect against cardiovascular events more than treatments that do not impact these factors. Moreover, aggressive treatment of dyslipidemia is critical to effectively manage the complications of diabetes.

However, despite the more favorable time-action profiles of modern insulin analogs, which can help optimize glycemic control, many patients remain suboptimally controlled. Even in teaching institutions throughout the U.S., American Diabetes Association treatment goals are only infrequently attained. For these reasons, the development of a novel, noninvasive, dry-powder insulin delivery system for inhalation use shows promise for adults with type 1 and type 2 diabetes.

Exubera

Exubera is an inhaled dry powder formulation of recombinant (rDNA) human insulin with a particle diameter of 1-5 μm . The powder is contained in blister packs and used in combination with an inhaler

device. There are two dosage strengths: each blister contains 1 mg or 3 mg of insulin brought up to a total weight of 5 mg with mannitol, glycine, sodium citrate, and sodium hydroxide. The inhalation system is designed to deliver a fine dry-powder formulation of regular human insulin deeply into the lung in a reproducible and efficient manner.

A blister pack is inserted into the inhalation device (similar to a nebulizer). A pneumatic mechanism is activated by a lever, which punctures the blister. The powder is dispersed in a discrete cloud into the air chamber. The insulin cloud is inhaled slowly, at the beginning of a deep breath. With a bioavailability of 10 to 15 percent and dose equivalence about three times greater than that of injected insulin, each administration delivers the equivalent of approximately 3 IU or 9 IU of subcutaneous (SC) insulin, respectively.

Early studies have shown promising results. Onset of action of inhaled insulin is faster than that of regular human insulin, more closely resembling onset of rapid-acting insulin analogs. Exogenously administered insulin by SC injection has several disadvantages when used in controlling prandial (meal-time) glycemia. Physiologic insulin secretion peaks 30 to 45 minutes after meals and then decreases to basal levels over the next two to three hours. Subcutaneous injection of regular human insulin causes plasma insulin to increase slowly with a peak level achieved 90 to 120 minutes following the injection, and then a slow decline to baseline approximately eight hours after injection. This leads to postprandial hyperglycemia followed by hyperinsulinemia and increased risk of hypoglycemia before the next meal. Although the rapid-acting insulin analogs have reduced some of these difficulties, another problem associated with SC insulin injections is the frequent inter- and intra-individual absorption variation. This appears more often in the

older, type 2 diabetes population, in whom absorption of rapid-acting insulin from SC sites has been shown to be slower than in patients with type 1 diabetes. Inhaled insulin is a viable alternative to prandial injectable insulin administration in patients with diabetes because of its more favorable pharmacokinetic profile and less invasive route of administration. In type 1 diabetes, inhaled insulin is used in combination with a longer-acting injectable insulin. In type 2 diabetes, inhaled insulin can be used as monotherapy, or in combination with longer-acting insulins or oral hypoglycemics.

Clinical Trials. Two 12-week clinical trials evaluated the effect of inhaled insulin in patients with type 1 or type 2 diabetes. These studies demonstrated that patient satisfaction is increased with inhaled insulin compared with injectable insulin. The data showed that improved patient satisfaction is consistently correlated with improvements in glycemic control.

The two 12-week trials were then extended to one year. Patient satisfaction and preference, along with effects on HbA1C levels with inhaled insulin, were compared with an SC insulin regimen both in patients with type 1 or type 2 diabetes. In the 12-week parent studies, patients were randomized to inhaled insulin or SC insulin regimen. In the one-year extension studies, patients were permitted to select their treatment regimen of choice. Patient satisfaction was recorded at baseline (beginning of parent studies), week 12 (end of parent studies), and one-year (extension studies).

Of the 60 patients who received inhaled insulin during the 12-week trials, 85 percent (n = 51) chose to continue treatment, 3.3 percent (n = 8) switched to SC insulin, and 1.7 percent (n = 1) did not continue in the trial. Of the 61 patients who received SC insulin in the 12-week studies, 21.3 percent (n = 13) chose to continue treatment, 75.4 percent (n = 46) switched to inhaled insulin, and 3.3 percent (n = 2) did not

continue. From baseline to one year, reductions in HbA1C of 0.8 percent were maintained, and greater improvements were noted in the subjects using inhaled insulin versus those in the SC insulin group, with overall satisfaction of 37.9 percent versus 3.1 percent, respectively.

The Lung as a Site for Insulin Delivery. The lung is an excellent site for drug delivery. The alveolar-capillary network, with a surface area of 140 m², is the body's largest microvascular organ and receives the entire cardiac output. Because the lung provides a large surface area for drug absorption, inhaled insulin rapidly attains peak plasma level and metabolic effect. The primary mechanism of insulin absorption across the alveolar capillary and epithelial cells remains unknown, but is believed to be transcytosis (i.e., "across the cells") and formation of insulin vesicles. In this process, insulin molecules are taken up in vesicles by the alveolar epithelial cells. These insulin-containing vesicles are released between epithelial cells and the alveolar capillary endothelial cells. Insulin molecules are then taken up within vesicles by endothelial cells, transported across them, and released into the alveolar capillary blood.

Pulmonary Delivery of Insulin. Following inhalation, pulmonary delivery of insulin results in peak insulin levels within 15 to 20 minutes, with return to baseline 40 to 60 minutes later. If inhaled insulin is not administered correctly, a large portion of the dose will deposit in the upper airways and subsequently be removed from the lung via mucociliary clearance. In order to be absorbed systemically, insulin must be deposited deep within the lung. Two major factors affect its optimal deep-lung deposition: particle size and particle velocity. The optimal particle size for delivery to the alveoli is 1 to 3 μ m in aerodynamic diameter. Larger particles will likely be deposited in the oropharynx and

upper airways, whereas smaller particles will be lost on exhalation. Independent of particle size, particle velocity also has a major effect on absorption. Inhaled insulin particles must have a low velocity for optimal deposition and absorption.

Safety. The safety of injected insulin is well documented. There is less data to support the safety of inhaled insulin, although in general, studies have confirmed that its safety is comparable with SC insulin. The incidence of hypoglycemia is similar. In animal studies with rats and monkeys, daily inhalation was well tolerated with no evidence of airway or pulmonary lesions.

The American Conference of Governmental Industrial Hygienists has determined that the threshold limit value for inhalation of insoluble "nuisance dust" into the lung is 30 mg/day. Inhaled insulin is rapidly absorbed from the epithelial surface of the lung and therefore will only deposit up to an average of 10 mg of insulin into the lung each day. This means that therapeutic daily doses of inhaled insulin would not be expected to adversely affect pulmonary function. In general, pulmonary function has been stable in patients with type 1 and type 2 diabetes who have been treated with inhaled insulin, and no clinically significant differences in common measures of pulmonary function (spirometry, lung volume, diffusion, capacity or oxygen saturation) have been noted.

An increase in the incidence of mild-to-moderate cough has been reported, which should be expected with inhalation devices. Cough tended to occur within seconds to minutes after insulin inhalation, and lessened with continued use.

Increased antibody formation has been reported with insulin analogs in general. The clinical impact, if any, of such increases has yet to be determined. Pooled data from Phase II and III (three- and six-month) studies of inhaled insulin in patients with type 1 and type 2 diabetes have demonstrated that

Table 2
Patient Advice for Exubera

- Read the *Medication Guide* provided by the manufacturer before you start using Exubera, and each time you get your prescription filled.
- This medicine should not be used if you smoke or have stopped smoking within the past six months. If you decide to start smoking, contact your doctor for a different treatment for your diabetes.
- Tell your doctor if you have unstable or poorly controlled lung disease, or are using any other inhaled medicine.
- This medicine is to be placed in the Exubera inhaler device and inhaled through your mouth into your lungs as directed. The manufacturer states that mealtime doses should be taken 10 minutes before a meal.
- Do not open the blister. The inhaler device will open it automatically. Do not swallow the powder or breathe into the inhaler.
- Follow your doctor's advice on diet, exercise, sleep, personal hygiene, and how to monitor your blood sugar.
- Tell your doctor about all other prescription and OTC medicines, vitamin/mineral supplements, natural products and herbal remedies you are taking. Some OTC medicines (decongestants, aspirin) have a warning on their label advising persons with diabetes not to take them unless directed by a doctor. If you see such a warning on the label of an OTC product, ask your doctor or pharmacist if it is okay for you to take the OTC product.
- Unopened blisters should be stored at room temperature, protected from moisture. Do not refrigerate, freeze or use them after the expiration date on the label.
- After opening the foil overwrap, follow the storage instructions in the *Medication Guide* and use this medicine within three months.
- The inhaler device can be used for up to one year from first use. The release unit should be changed every two weeks.

switching from SC insulin to inhaled insulin is associated with increased antibody levels. However, these increased antibody levels have not caused a need for increased insulin doses or allergic reactions.

Factors that Affect Inhaled Insulin Activity

Smoking. Smoking is reported to be as common in persons with diabetes as in the general population, and is known to increase the permeability of the alveolar-capillary barrier in humans. Smoking may therefore increase absorption of inhaled insulin such that its dose requirements may be lower in smokers. In comparison, SC insulin absorption is decreased in smokers, necessitating larger SC doses. Exubera is contraindicated in patients who smoke or who have discontinued smoking less than six months prior to starting therapy.

Lung Disease. In persons with underlying lung disease such as asthma, COPD, or upper respiratory infections (URI), delivery of inhaled insulin to the blood may be affected by the overall efficiency of pulmonary function. For example, a study showed that subjects with chronic asthma absorb less insulin after inhalation than healthy subjects, resulting in less action to reduce blood glucose levels. The decreased insulin absorption is believed to be caused by a difference in the airway caliber or pulmonary vasculature as a result of chronic lung disease. The patient's physician may suggest that inhaled insulin not be used during intermittent URIs.

Counseling Patients on Inhaled Insulin. A comprehensive *Medication Guide* is provided with Exubera. Patients should understand all the information before beginning therapy. A summary of these points, which pharmacists may use in their counseling, is provided in Table 2.

Overview and Summary

The benefits of intensive insulin therapy have been demonstrated in large clinical trials. Despite such advantages, intensive insulin therapy is not widely accepted because of real or imagined barriers to invasive insulin. Inhaled insulin is a non-invasive method of supplying insulin that should alleviate some of the problems and/or fears associated with insulin injections. It has demonstrated efficacy in terms of achieving significant attainment of HbA1C targets in both type 1 and type 2 disease. Inhaled insulin is, therefore, a suitable alternative to injectable insulin to promote achievement of good glycemic control, and therefore help to prevent the microvascular, macrovascular, and neuropathic complications of diabetes and decrease the risk of premature death.

Once inhaled insulin is made available, it may be of particular benefit in patients who are unreceptive to multiple daily insulin injections. It represents a promising and novel diabetes therapy that offers the benefit of noninvasive administration, along with a time-action profile that combines the advantages of both rapid-acting insulin analogs and regular human insulin.