The prevalence of diabetes is increasing at alarming rates worldwide. An estimated 194 million people are affected with diabetes, a figure the World Health Organization (WHO) expects to rise to 366 million by 2030.\textsuperscript{1,2} Insulin has long been a therapy for controlling blood glucose in people with diabetes and is the most effective glucose-lowering agent available. This is because it can be continuously titrated until glycemic goals are met. Individuals with type 1 diabetes require insulin replacement therapy from the onset of the disease and throughout their lives. Type 2 diabetes is a progressive disease normally resulting from a combination of insulin resistance and progressive beta-cell dysfunction, and is treated by most physicians in a stepwise manner.\textsuperscript{3} Management of type 2 diabetes typically begins with lifestyle interventions—i.e. diet and exercise—eventually followed by the addition of a single oral antidiabetic drug, then a combination of oral drugs. In the latter course of type 2 diabetes, patients need to add insulin replacement therapy to their treatment regimen.

Diabetes is associated with the development of micro- and macrovascular complications. Thus, the longer a person lives with uncontrolled diabetes, the greater the risk of developing vascular complications, including retinopathy, end-stage renal disease, neuropathy, and coronary heart disease. Major landmark clinical studies, such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), have shown that improvement in blood glucose control reduces the risk of development of diabetes-related complications.\textsuperscript{4-6}

The American Diabetes Association (ADA) recommends that people with diabetes achieve a glycated hemoglobin (HbA\textsubscript{1c}) <7\% for optimal diabetes control, although more stringent glycemic goals (i.e. HbA\textsubscript{1c} <6\%) may further reduce complications at the cost of increased risk of hypoglycemia.\textsuperscript{7} However, data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2000 suggested, if anything, a decrease in the percentage of persons achieving glycemic target.\textsuperscript{8} At the same time, the percentage of individuals treated with insulin either as monotherapy or in combination with oral agents remained essentially unchanged. Since these initial findings, additional data have suggested a slight improvement in glycemic control, but the majority of individuals with diabetes still do not achieve the goal of HbA\textsubscript{1c} <7\%.\textsuperscript{9}

A major limitation of intensive insulin therapy is that in order to optimize glucose control, the regimen may require multiple insulin injections that, in turn, may increase the complexity and effort required to comply with the regimen. Intensive insulin therapy has not achieved widespread acceptance because of barriers to its use from both patients and physicians.\textsuperscript{10-13} Consequently, providers who care for patients with type 2 diabetes may accept less than optimal control on combination oral therapy because of these concerns or the concerns relayed to them by the patients. In this regard, there has been great interest in developing alternative means to deliver insulin. Attempts have included transdermal, nasal, and buccal approaches.\textsuperscript{14} However, the approach that has attracted the most interest based on success to date is insulin delivered by pulmonary inhalation. The efficacy of inhaled insulin and its potential clinical applications are discussed in this review. Although a number of devices are in development, Exubera (insulin human [rDNA-origin] inhalation powder, Pfizer/Nektar Technologies) is the only product commercially available.

**The Concept of Inhaled Insulin**

Efforts to develop non-invasive alternatives to injectable insulin began soon after the discovery of insulin. Until recently, problems with insulin bioavailability and the technology required for delivering insulin by alternative routes have hindered progress.\textsuperscript{15} The pulmonary route is the most widely researched non-invasive alternative to subcutaneous administration, and offers the greatest potential for systemic insulin delivery. Its advantages include a large absorptive surface, high permeability, and an extensive vascular network permitting rapid passage of insulin from the alveoli into the systemic circulation.\textsuperscript{16}

Based on the feasibility of delivering insulin via pulmonary inhalation, there are a number of devices and insulin formulations currently in development for pulmonary delivery including Exubera (Pfizer/Nektar Technologies), AIR insulin system (human insulin inhalation powder, Eli Lilly/AIkermes), AERx iDMS (liquid human insulin formulation, Novo Nordisk/Andigim), and Technosphere Insulin (human insulin dry powder, MannKind) pulmonary insulin delivery systems. The only inhaled insulin that has been approved thus far is Exubera, a fast-acting dry-powder formulation of human insulin intended for use before meals. The major differences in the systems in development include the insulin formulation used—for example dry powder...
Inhaled Insulin

versus liquid—and the specific mechanics of the devices.

In early 2006, Exubera obtained US and EU marketing approval for the treatment of adults over 18 years of age with type 2 diabetes not adequately controlled with oral antidiabetic agents and requiring insulin therapy. Exubera is also indicated in addition to long- or intermediate-acting injectable insulin for the treatment of adult patients with type 1 diabetes, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns.

Efficacy of Inhaled Insulin

The pharmacokinetic profile of all the insulin formulations mimics the normal physiological pattern of insulin secretion in response to a meal, with an initial rise in plasma insulin levels similar to rapid-acting insulin analogs. Therefore, inhaled insulin is a prandial insulin and should be administered 10 minutes before meals to provide post-meal glucose control.

The efficacy of inhaled insulin has been investigated in both type 1 and type 2 diabetes. Studies conducted in patients with type 1 diabetes compared pre-prandial with conventional insulin regimens, intensive insulin dosing, and fast-acting insulin options such as insulin lispro. For the most part, these studies demonstrate comparable glycemic control between subcutaneous insulin regimens and regimens incorporating pre-meal use of inhaled insulin.

The efficacy of inhaled insulin in the treatment of type 2 diabetes has been compared with oral agents and with a subcutaneous rapid-acting insulin program. When used as an early pharmacological intervention, Exubera achieves blood glucose control in patients with type 2 diabetes not optimally controlled on diet and exercise alone. Similarly, two studies showed that, in patients not adequately controlled on a single oral agent (HbA1c >9.5%), addition of Exubera significantly improved glycemic control compared with adjunctive oral agent therapy. Furthermore, in subjects failing dual oral antidiabetic therapy, Exubera provides greater improvements in blood-glucose control when administered alone, or in addition to, existing oral therapy. In clinical trials, Exubera was also shown to be effective as part of a conventional insulin program, achieving levels of blood-glucose control comparable to subcutaneous insulin injections.

Safety and Tolerability

The safety profile of all inhaled insulin formulations will need to be shown in long-term clinical studies. Observations with Exubera suggest that the adverse event profile throughout the clinical development program was generally mild to moderate in severity, and discontinuation rates were low. As with all insulin products, hypoglycemia was the most commonly reported adverse event, with severity and incidence similar to those observed with subcutaneous insulin therapy. As expected, the incidence of hypoglycemia was higher with adjunctive Exubera compared with adjunctive oral antidiabetic therapy. Coughing of mild to moderate severity has been observed at a higher frequency in subjects receiving Exubera compared with those receiving subcutaneous insulin. Coughing generally occurred within seconds to minutes of inhaled insulin administration, was rarely productive, and decreased with time on therapy. Fewer than 1% of trial participants discontinued Exubera because of coughing.

There have been observations of small but consistent treatment group differences in lung function tests—forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO)—with Exubera. However, as well as being small, these changes occurred soon after treatment initiation, did not progress for up to two years, and were reversible following discontinuation. Obtaining an FEV1 is recommended prior to Exubera initiation and at regular intervals thereafter in order to detect any unexpected increased effect.

Clinical Applications of Inhaled insulin

One of the more important uses of inhaled insulin will be in individuals with type 2 diabetes, especially those who fail combination oral therapy. Regimens using pre-prandial inhaled insulin along with one injection of basal insulin have been shown to be comparable to conventional insulin injection regimens (mixed regular/neutral protamine hagedorn insulin) in subjects with type 2 diabetes. However, it has also been reported that patients with either type 1 or type 2 diabetes receiving inhaled insulin have reported enhanced overall satisfaction, quality of life, and acceptance of intensive insulin therapy.

Conclusion

While not the sole answer to the problem with compliance and inadequate glycemic control commonly seen in clinical practice today, the insulin inhaler should be considered another therapeutic option available to the clinician. Insulin administered by pulmonary inhalation has been demonstrated to be an effective therapy compared with subcutaneous insulin regimens in patients with both type 1 and type 2 diabetes, and appears superior compared with failed oral therapies in patients with type 2 diabetes.