Exhuberance Over Exubera

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Near the turn of the 20th century, the body of scientific knowledge surrounding diabetes was formidable enough to enable a major discovery. It is important to place yourself in that time and sense the fever of those working on a discovery that could save lives and enable a new product to be produced. The potential was as great as a cancer or AIDS cure would be today. In 1901 Eugene L. Opie demonstrated the association between degeneration of segments of the pancreas and the formation of diabetes, and in 1912 Aldo Massaglia demonstrated that destruction of pancreatic segments resulted in glycosuria.[1,2] In 1916 Nicholas C. Paulesco observed that intravenous pancreatic extract given to a diabetic dog was followed by rapid and short-lived symptomatic relief. In later experiments, he demonstrated reductions in ketones, urea, and urine volume.[1] These findings were published in June 1921.[1]

Independently, a surgeon (Frederick Banting) and a medical student (Charles Best) working at the University of Toronto found much the same results but also demonstrated that an overdose of the extract produced signs and symptoms of hypoglycemia.[1–3] In 1922 Banting and Best prepared a thick brown extract of beef pancreas, administered it to a 14-year-old patient named Leonard Thompson, and saved his life.[1–3]

From then on, there was no holding back. Major innovations in insulin products have occurred regularly since its initial use in the 1920s. In the 80 years insulin has been mass-produced, there have been three phases of advance: *1*) the modification of insulin, *2*) the purification of insulin, and *3*) the production of human insulin.[1]

Modification of Insulin

The original insulin produced was short-acting and required frequent administration. Therefore, scientists set out to alter the duration of action, onset, and peak of insulin to increase patient compliance.[1] Adding zinc or protein to the insulin structure extended the duration of action.[1] Patients would not need as many doses per day, which would increase compliance and satisfaction with insulin therapy. Table 1 shows when various formulations of insulin were introduced.[1]

Formulations continue to be developed that provide variations in the onset, peak, and duration of action for insulin. Recently, modifications of the insulin structure have produced analogs of human insulin that permit delivery of insulin that better approximates normal physiology.

Purification of Insulin

Researchers soon realized that insulin would need to be further purified because of its adverse effects. The main side effects included insulin allergy, lipoatrophy at injection sites, insulin antibody formation, increased insulin requirements because of insulin resistance, altered metabolic control, placental transfer of insulin antibodies, autoimmunity, and late diabetes complications (vascular changes).[1]

To decrease these side effects, Banting and Best tried recrystallization of insulin.[1,2] This helped decrease all of the side effects except antibody formation, which was later improved using ion-chromatography.[1,2] Today, these allergic reactions have been almost eliminated from insulin therapy.

Production of Human Insulin

In 1960, it was discovered that human insulin and animal insulin amino acid sequences were different.[1] Scientists began to wonder whether human insulin could be developed and could result in fewer complications for patients.[1]

Subsequently, four different methods for preparing human insulin were developed. The first was the use of human cadaveric pancreas.[1] These were a limited resource, so this method was used mainly for testing patients with insulin allergy.[1] In 1974, Seiber et al. successfully initiated the second

IN BRIEF

The isolation, purification, and clinical use of insulin has been enhanced many times in the past 80 years. This article outlines the development of insulin and describes the formulation, activity, and practical use of a newly approved inhaled form of insulin sold under the trade name Exubera.

Table 1. Insulin Formulation Timeline

Protamine insulin	1936
Protamine zinc insulin	1936
Surfen insulin	1938
Globin insulin	1939
Isophane insulin	1946
Lente insulin	1951
Biphasic insulin	1959

method: total peptide synthesis from amino acids.[1] A single clinical trial was done, but because of the expense of this method and limited resources, this technology could not be implemented on a large scale.[1] The third method was enzymatic conversion of porcine insulin to human insulin, described in 1978.[1] This method proved to be quite successful, yet scientists wanted a formulation that was completely human. Tests were continued, and in 1981 recombinant DNA technology was used to derive a human insulin that had fewer contamination issues that any previously developed formulation.[1]

Inhaled Insulin

Against this backdrop of technological advances, inhaled insulin (the first of which to reach market sold by Pfizer under the trade name Exubera) is the latest in diabetes drug delivery technology. Many companies (Aerogen, Aradigm/Novo Nordisk, Biosante Pharmaceuticals, Coremed, Lilly/Dura Pharmaceuticals, KOS Pharmaceuticals, MannKind Corporation, Nektar Therapeutics/Pfizer, and Qdose) are developing additional inhaled insulin products.[4] Although other new drugs use this same technology (tobramycin, dronabinol, parathyroid hormone), none have the potential to be as useful or would increase patient ease of use as much as inhaled insulin.[5]

Nektar Therapeutics has developed a method of delivering macromolecules using the lungs as the drug route.[5] When developing the new dosage form for insulin, researchers used glass stabilization to increase the stability of insulin.[5,6] Glass stabilization does not really involve glass, but rather sugars that make "glassy shields" to protect fragile protein medications from being denatured by various compounds until they are absorbed into the bloodstream.[7] The technology of changing the sugars into a glassy substance is called vitrification and was discovered in the late 1980s independently by two scientists, Carl Leopold and Felix Franks.[7]

Nektar Therapeutics has now applied vitrification to insulin. Insulin is coated with sugars and then sprayed into a dispersion of particles. The dried particles measure 3 μm in diameter, a size feasible for deposition in the alveoli.[7,8] Once in the lung, these tiny sugary spheres are dissolved and diffuse into the bloodstream quickly.[7,8]

Effectiveness of Inhaled Insulin

Exubera is recombinant-engineered human insulin. After the powder is delivered to the alveoli, approximately one-third of the administered dose is absorbed into the bloodstream. The onset of inhaled insulin acts as quickly as subcutaneously administered rapid-acting insulin and more quickly than subcutaneous regular insulin. Peak insulin levels are achieved at a mean of 49 minutes (range 30–90 minutes) with Exubera compared to 105 minutes (60–240) with regular insulin.[9,10] Table 2 contains information about insulin and other products used for rapid glucose reduction.

Inhaled insulin, despite some controversy, provides patients with a new option for achieving lower hemoglobin A_{1c} (A1C) levels and thus preventing or delaying the onset of complications.[11]

Overall, studies have shown that inhaled insulin has comparable efficacy to injectable regular insulin. In fact, most studies report a greater reduction in A1C and fasting plasma glucose with inhaled insulin compared to injectable insulin. Studies have shown that when inhaled insulin, combined with basal insulin, is compared to an injectable-only regimen in patients with type 1 diabetes, A1C at 24 weeks is slightly lower in the inhaled-insulin patients. Fasting blood glucose was shown to be an average 25 mg/dl lower with inhaled insulin than with a conventional insulin regimen. Patients taking inhaled insulin had fewer hypoglycemic episodes than patients taking injectable insulin.[12]

In type 2 diabetes, similar results have been shown. Patients whose diabetes was uncontrolled on one oral agent were randomized to receive either an additional oral agent of a different class or a premeal regimen of inhaled insulin. After 12 weeks, patients on inhaled insulin showed a greater reduction in A1C than those on oral agents alone. In one study, patients were randomized to receive inhaled insulin plus one oral agent or two oral agents. The study continued for 2 years. The mean A1C was reduced from 9.6 to 7.7% in patients on inhaled insulin versus a reduction from 9.6 to 8.1% in patients on oral agents alone.[13]

An additional 12-week study[14] showed that starting inhaled insulin reduced A1C from 9.8 to 7.5% compared with a 0.1% reduction in patients continuing on the oral regimen. Results showed that 34% of patients receiving inhaled insulin reached an A1C of < 7.0%, whereas none of the patients remaining on oral agents alone reached the same goal. These data demonstrate the potential benefit of inhaled insulin in type 2 diabetic patients whose diabetes is uncontrolled on oral agents alone.

Table 2. Pharmacokinetic Profiles of Short-Acting Insulins

	Time Relative to Food (minutes)	Onset (minutes)	Peak (minutes)	Duration (hours)
Inhaled insulin (Exubera)	10	30	30–90	6
Regular insulin	30	30–60	120–180	6–8
Lispro	15	15	30–90	4–6
Aspart	15	15	45	3–5
Glulisine	15–30	Rapid	30–90	1–2.5

Initiating Inhaled Insulin

Before initiating this new technology, clinicians must determine how to dose it and what the equivalent dosing is to other insulins. Initial premeal doses are calculated by using the formula: body weight (kg) × 0.05 mg/kg = premeal dose (mg) and rounding down the dose to the nearest whole milligram.[15] Table 3 is adapted from the package insert for Exubera.[15]

Exubera is packaged as a powdered substance in small foil reservoirs called blisters. Blister sizes should be combined in order to use the fewest blisters possible. Because of this dosing recommendation, when patients purchase this medication, a combination of blister sizes will need to be dispensed.

In initiating inhaled insulin, it is helpful to understand how it compared to other forms of insulin. To date, it has been compared to regular insulin, although it works more like rapid-acting insulin.

Table 4 suggests that a 1-mg blister of Exubera inhaled insulin is ≅ 3 IU of subcutaneously injected regular human insulin. A 3-mg blister is ≅ 8 IU of subcutaneously injected regular human insulin.[15] Note that inhaling multiple 1-mg doses will not provide the same response as combinations of 1- and 3-mg packs because of differences in the percentage of the dose delivered from each blister.[15] Up to 45% of the 1-mg blister contents and 25% of the 3-mg blister contents may be retained in the blister.[16]

Table 3. Approximate Guidelines for Initial Premeal Exubera Dose[15]

Patient Weight (kg)	Patient Weight (lb)	Initial Dose per Meal (mg)
30–39.9	66–87	1
40–59.9	88–132	2
60–79.9	133–176	3
80–99.9	177–220	4
100–119.9	220–264	5
120–139.9	265–308	6

Table 4. Approximate Equivalent IU Dose of Regular Human Subcutaneous Insulin for Exubera Inhaled Insulin Doses Ranging from 1 to 6 mg

Dose (mg)	Approximate Regular Insulin Subcutaneous Dose (IU)	Number of 1-mg Exubera Blisters per Dose	Number of 3-mg Exubera Blisters per Dose
1	3	1	—
2	6	2	—
3	8	—	1
4	11	1	1
5	14	2	1
6	16	—	2

Tools for Patients Starting Inhaled Insulin

Exubera prescriptions will be dispensed with a medication guide containing U.S. Food and Drug Administration (FDA)-approved information written especially for patients.[10] The medication guide is thorough and written on a sixth-grade reading level. The comprehensive guide includes instructions to patients on the proper use and cleaning of the device, as well as a problem troubleshooting guide. It also lists precautions patients should take in proper diabetes management and supporting information on diet, glucose monitoring, and other parameters necessary for its proper use.

The guide is complicated enough that patients should not be left on their own to learn to use the device, which could lead to frustration. The authors recommend a session with a diabetes educator to allow patients to practice their technique, ask questions, and watch someone else who knows the device well demonstrate its proper use. It is feasible to think that patients with reduced vision could learn to use the device with repeated teaching and practice, providing a means for tighter insulin control without injections for these patients.

The delivery device has been designed to help ensure ease of handling, build in safeguards, and help prevent variance from one patient to another. Judgment on the durability and transportability of the product will come with time.

Monitoring Parameters

Clinical trials with Exubera have included > 2,000 patients treated for > 6 months. Of most concern is the likelihood that serum glucose response to the agent may not be predictable or will vary within the regimen for a given patient. Therefore, patients should carefully monitor their blood glucose often to aid in optimizing dosing.

Side effects identified in clinical trials of Exubera have included increased cough, pharyngitis, rhinitis, and sinusitis (ranging in incidence from 5 to 10%). Side effects with lower incidence included shortness of breath (4%), otitis media (6.5%), ear pain (3.9%), and dry mouth (2.4%).[9] Several of these conditions could have been associated with seasonal illness.

Some patients have reported a cough within seconds to minutes of product inhalation; such episodes occurred less frequently as treatment continued.[17] A weight gain of 2.8 kg (6.16 lb) occurred in patients on inhaled insulin monotherapy, and a gain of 2.7 kg (5.94 lb) occurred in those taking inhaled insulin and an oral hypoglycemic agent in combination, compared to no weight gain in

those continuing oral therapy alone.[4] A small nonprogressive difference in pulmonary function tests was also observed between a limited group of Exubera and control patients. Additional studies are being conducted to address this safety concern and determine the long-term pulmonary safety profile of this product.[10]

Because this new form of insulin enters the bloodstream through the lungs, patient monitoring includes pulmonary function tests via spirometry (forced expiratory volume [FEV]), which should be performed before beginning therapy with inhaled insulin, at 6 and 12 months after initiation of therapy, and annually thereafter. A small asymptomatic decrease in lung function should be expected; however, it should not progress with further testing. The presence of pulmonary symptoms such as cough, dyspnea, and wheezing may indicate the need for more frequent monitoring.[15] If spirometry tests show a decline in FEV over 1 second (FEV1) ≥ 20% from baseline, the test should be repeated. If results are confirmed and the decline in FEV1 remains ≥ 20% from baseline, Exubera should be discontinued.

Candidates for Inhaled Insulin Use

Exubera has been tested and shown to be effective and safe in both type 1 and type 2 diabetic patients. The safety, efficacy, and activity of the insulin in this product allow it to be used alone, with oral agents, or with longer-acting insulin products. It could be a welcome addition to the range of available insulin products for people who choose not to use insulin injections or who find injections difficult. Inhaled insulin will best suit patients who require multiple daily injections and who are having problems with injections.[16]

Exubera is not appropriate for use in patients < 18 years of age because of lack of clinical trials in this population. It is not to be used in patients who smoke or have stopped smoking in the past 6 months because the drug exposure increases two- to fivefold in this population. The same is true for patients who may begin smoking or return to smoking. It should not be used in patients with history of significant lung disease. It can be used in patients > 65 years of age. The agent still has category C classification, which means there are not enough data to show that its use is safe during pregnancy. It has not been used in trials involving patients with significant renal or hepatic disease.

Additional Considerations

How much of a breakthrough is inhaled insulin, which is, after all, the same drug as standard injectable insulin? Does the potential benefit of improved adherence outweigh the higher cost of this form of insulin? These are common questions that may be under consideration among third-party health care payers.

Clinical data have shown increased patient acceptability with inhaled insulin compared to injectable insulin. In one randomized controlled trial, type 2 diabetic individuals were educated about and presented with inhaled insulin as a treatment option. Results showed a threefold increase in the number of patients who would choose insulin therapy as augmentation in glycemic control. Of those, the majority of patients chose inhaled insulin as the option. These results suggest a high potential for more patients to have better glycemic control, thereby reducing microvascular and macrovascular complications and leading to improved quality of life.[18]

Similar results have been reported regarding patient satisfaction with inhaled insulin. Several clinical trials have proven a clinically significant difference in treatment satisfaction with inhaled insulin compared to conventional injectable insulin regimens.[12,19,20] A *Chicago Tribune* article[21] reported that "inhaled insulin was rated higher with regard to ease of administration, comfort, convenience, time of dosing, flexibility of eating schedule, and ease of taking insulin many times per day; however, patients using subcutaneous insulin were less self-conscious about taking insulin away from home." Finally, there have been fewer documented hypoglycemia episodes in type 1 diabetic patients who were taking inhaled insulin compared to those using injectable insulin.[12]

Analysts project a $4-per-day cost associated with Exubera. This could be up to four times more expensive than injectable insulin.[21] The jury is still out regarding insurance coverage of this new insulin formulation. For third-party payers, it may represent a new option for long-term cost reduction if the expected improvements in adherence are realized in nonclinical trial settings. On the other hand, health insurers may see this as merely a new formulation of an old drug. Most analysts agree that if health insurers decide to cover inhaled insulin, it will most likely be on the most expensive tier of the formulary, resulting in a high copayment for patients.[21,22]

Nonetheless, inhaled insulin is a dramatic breakthrough in insulin delivery. Although there are safety and cost considerations, it also offers potential adherence and satisfaction advantages. Whether those added benefits are worth the extra expense is a decision to be reached between clinicians and their patients.

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