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MEETING PROCEEDINGS

Inhaled Insulin: Promises and Concerns

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Abstract

Since the introduction of Pfizer Exubera® in the early 1990s, a number of other inhaled insulin solutions have been developed. This article provides an overview of inhaled insulin systems developed by Pfizer, Novo Nordisk, MannKind, and Lilly, three of which are currently in phase 3 trials. The strengths and weaknesses of each product, as well as the general technologies (liquid vs dry powder), are evaluated. Results of clinical studies conducted by Pfizer and corroborated by other studies are summarized. Although inhaled insulin promises much, a greater body of controlled studies is necessary to draw firm conclusions about its safety and efficacy.

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Introduction

Inhaled insulin presents a very exciting and new subject with many questions because many promises have been made. Now there are also many concepts regarding this new therapy, and we have to predict what is going to happen to this new treatment for diabetes.

It is a long story that started as early as 1925, but nothing really happened until the late 1990s when inhaled insulin (Pfizer Exubera® project) came on the market in the United States for a few months, as well as in some European countries, such as Ireland and Germany. Now there are three other projects in phase 3: (1) the AERx®, Novo Nordisk, Aradigm inhaler, (2) the Technosphere®, MannKind, MedTone inhaler, and (3) the AIR®, Lilly, Alkermes inhaler. The others are less advanced projects (Generex, Dura, Kos, Elan, etc.).

Rationale for Pulmonary Route

The pulmonary route is the only route that can absorb enough insulin with the best bioavailability without promoters. **Table 1** gives an overview of alternative routes that avoid injections with the percentage of bioavailability, which is the major obstacle. Promoters make membranes more permeable, although they are always toxic and, like other surfactants, are tolerated very poorly. Because of its huge surface, which is almost the surface of a tennis court, the pulmonary route is thus the only route that does not need a surfactant or promoter to be effective enough. However, the real problem is getting the insulin particles down to the alveoli. Usually with most of the inhaler devices, insulin particles stop, either in the mouth or in the bronchial system. To get down to the deep lung, it is necessary to have a special, very precise diameter of each particle, which is why it was so difficult to design a good device for an inhaler.

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Abbreviations: (COPD) chronic obstructive pulmonary disease, (FEV1) forced expiratory volume in 1 second, (DL_{CO}) carbon monoxide diffusing capacity, (HbA1c) hemoglobin A1c, (PFT) pulmonary function test, (PWD1) persons with type 1 diabetes, (PWD2) people with type 2 diabetes

Keywords: cough, diabetes, inhaled insulin, inhaler, pulmonary function

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Rationale for Use in Diabetes

Intensive insulin treatment of type 1 diabetes requires at least four insulin injections daily. Thus, a number of persons with type 1 diabetes (PWD1) are upset not only by problems of diet, restrictions, and hypoglycemia, but also because of multiple daily needle injections. The problem in people with type 2 diabetes (PWD2) requiring insulin secondarily is often the fear of insulin injections. Because there is a huge proliferation of possible noninsulin medications, it is even getting harder and harder to convince the patient to use insulin. However, one of the major reasons why patients tend to delay the beginning of insulin is needle injection. If we can avoid or bypass that problem, then we may persuade patients to get insulin therapy earlier and therefore get better blood sugar control.

Projects: Technical and Physiological Differences

The Pfizer/Aventis/Nektar Exubera inhaler (**Figure 1**) is supposed to deliver insulin after deagglomeration of insulin dry powder that the patient should inhale. The inhaler thus needs a lot of energy and space, which is why the device is so large. Exubera blisters contain either 1 or 3 milligrams of insulin powder, which is equal to 2 or 8 units, consecutively. In a release unit, puncturing the blister makes a cloud and Exubera is then released into the chamber. Many patients have to use many blisters at a time to get their full meal dose of insulin, which is a disadvantage of that system.

The Novo Nordisk AERx system (**Figure 2**) is a device that uses single-use strips of liquid insulin, which deliver up to 10 units of insulin per strip (**Figure 3**). The patient can dial the dose and go by increments of 1 unit. However, with one strip, patients waste a lot of insulin using the low dose each time they puncture the strip. There is a memory in the device. Thanks to a guidance system, the insulin available in the system is to be inhaled only at the right moment—when the patient breathes normally, deeply enough.

MannKind Corporation Technosphere/insulin (**Figure 4**) uses dry powder with low-density particles and 29%

Table 1.
Alternative Routes to Avoiding Injections

	Bioavailability without promoter	Bioavailability with promoter
Nasal	2	5–40
Rectal	3	40
Buccal	0.7	25
Conjunctival	0.3–6.6	40
Pulmonary	8–30	100

Figure 1. The Pfizer/Aventis/Nektar Exubera inhaler.

Figure 2. AERx.

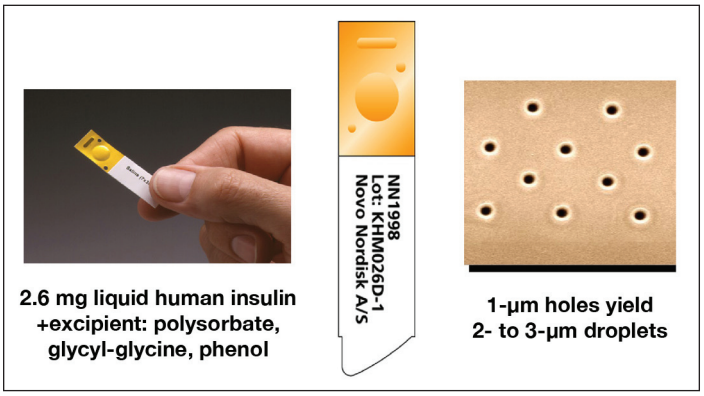

Figure 3. AERx insulin diabetes management system single-use insulin strip.

Figure 4. Technosphere/insulin.

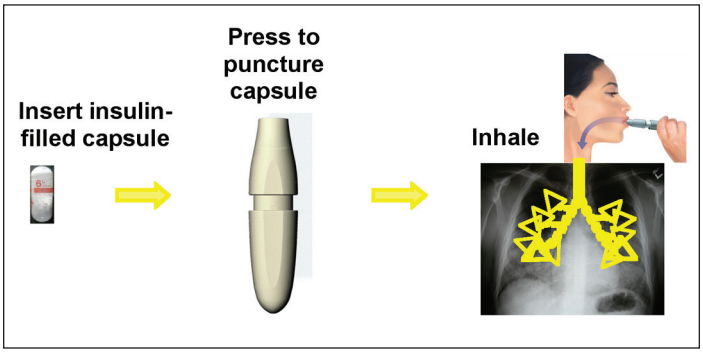

Figure 5. Lilly/Alkermes AIR inhaled insulin system.

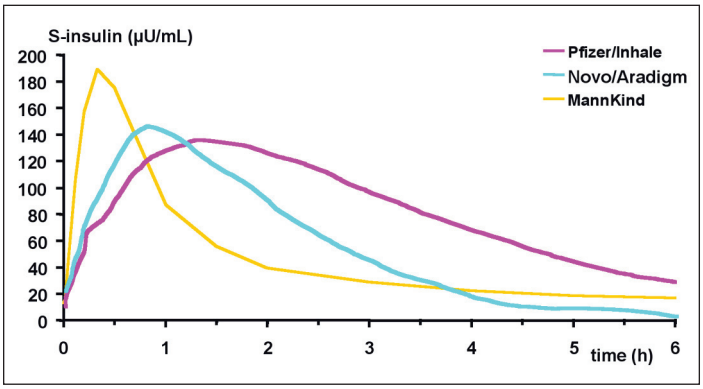

Figure 6. Inhaled insulin pharmacokinetics.

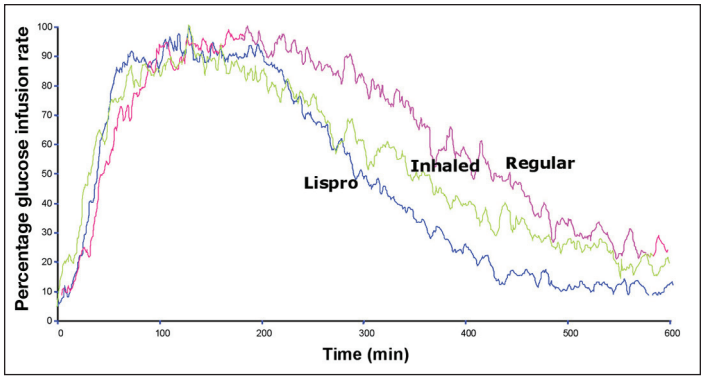

Figure 7. Pharmacodynamics of inhaled insulin. Graph courtesy of Dr. Lutz Heinemann, Profil Institute for Metabolic Research, Neuss, Germany.

bioavailability. The cartridge is manufactured by units; a 15-unit cartridge is equal to 5 IU and a 30-unit cartridge is equal to 10 IU (increments are by 5 insulin units).

The Lilly Alkermes system (**Figure 5**) is also a dry powder system that uses light, large particles that float better and get to the deep lungs better. The capsules have multiples of either 2 or 6 units, with increments of 2 units at a time.

Overall, an advantage of the dry powder systems is that they are a more stable, less sophisticated device. Disadvantages include having more complex formulations, drug carrier toxicology, and possibly higher immunogenicity. Advantages of liquid technology include simple insulin formulation, easier dosing, and possibly lower immunogenicity. Disadvantages of liquid technology are particularly dependent on aerosol particle stability on humidity and temperature; acceptable bioavailability requires sophisticated devices. **Table 2** gives an overview of technical differences that are important for patients, such as the size of the device, increments used for insulin dosing, and insulin storage. Physiologically, no major difference exists between insulin even in the manufacturers' claim differences. MannKind insulin is supposed to start earlier and finish its action within 2 hours; the others start a little bit later, but earlier than the usual short-acting analogs (**Figure 6**). **Figure 7** reflects a real profile of activity in terms of pharmacodynamics, which is the amount of glucose needed to be infused to make normal glycemia. Inhaled insulin seems to be as fast as lispro, but almost as slow to finish as regular insulin (**Figure 7**).

Other important factors are intersubject and intrasubject variabilities, which have not been improved with inhaled insulin. Although the devices are very sophisticated, insulin absorption is gross from day to day with every patient, particularly also with inhaled insulin.

Table 2.
Technical Concerns for Patients

	Pfizer	Novo Nordisk	MannKind	Lilly
Device	Large	Heavy	Small	Small
Unit increment	3	1	5	2
Insulin storage	Ambient	Refrigerator	Refrigerator	Ambient

Efficacy: Available, Ongoing, and Missing Studies

The Pfizer studies have the most clinical experience, but other clinical studies have confirmed the Pfizer studies. The Pfizer studies have been done now since 2000, but only on specific patients—nonsmokers, nonchronic obstructive pulmonary disease (COPD), and nonasthma patients—and only on adults. Smoking increases lung absorption; COPD and asthma may decrease absorption.

One of the most important type 2 studies is the comparison of Exubera with oral agents showing that inhaled insulin works better than oral agents when oral agents fail. If some oral agents are added, Exubera even works a little bit better. In insulin-treated PWD2 after 2 years the results are the same. In terms of efficacy, inhaled insulin does not do worse and does not do better.

There are many studies being done in type 1 diabetes. Unfortunately, the control arm is almost always neutral protamine Hagedorn and regular insulin. In both cases (subcutaneous versus inhaled), patients' hemoglobin A1c (HbA1c) levels dropped by just 0.3% (patients went down from 7.8 to 7.5%). However, these are the studies that Pfizer has decided to pursue now and they are very important. They are most directed at safety issues or subgroup issues, such as the long-term pulmonary function test (PFT) study and long-term lung tolerance studies. Unfortunately, some data look negative at the bronchial–alveoli level. What is missing in type 1 diabetes are some good studies versus current analogs, versus pumps, and versus pens. In type 2 diabetes, a group study versus bedtime insulin still needs to be done.

Safety: Hypoglycemia, Cough, and Lung Function

In safety studies, there is no improvement but no worsening of hypoglycemia in PWD1. In PWD2, hypoglycemic events are less frequent, and in subcutaneous insulin versus inhaled insulin, there was no difference even after 2 years.

Ten to 16% of patients initially had some minor problem with cough in terms of a mild, dry, nonproductive throat cough that tended to fade away. The cough often results from irritation of the product on the back of the throat and tends to get better if patients drink right after they inhale. Only 1% of the patients withdrew from studies because of persistent cough.

More importantly is the possibility of fibro disease or anatomical deterioration of the lung tissues by product inhalations. Pfizer performed computed tomography (CT) scans in several patients. The CT scans were normal at baseline and stayed normal in the majority of the patients after 2 years. On Exubera, there may be changes from baseline to 2 years, which are always similar with the control group, so there is no significant difference between the two groups in terms of high-resolution CT changes. Carcinogenicity is a major issue, especially in ex-smokers. They found three cases of lung cancer among Exubera-treated patients over the entire several thousand patients' experience. The difference is not significant, as they were expecting 6.99 patients, according to their age, to the number of cases. Thus, there is no indication that inhaled insulin is carcinogenic.

Lung function is a major concern and has been widely discussed recently. There have been hundreds of PFTs performed in patients. Mean treatment group differences between Exubera and comparators over the 2-year period were small in magnitude with a slight decrease in forced expiratory volume in 1 second (FEV1) of about 40 milliliters (mean baseline FEV1 was approximately 3 liters). It is a reversible nonprogressive, minor reduction of FEV1 that does not aggravate after 2 years of continuous therapy and, most importantly, recovers during the washout phase. The normal degradation of FEV1 as a consequence of age is about 40 milliliters per year. Carbon monoxide diffusing capacity (DL_{CO}) as an objective measurement of lung function also degraded slightly in the inhaled group but then stayed stable. The change from baseline (FEV1 and DL_{CO}) did not correlate with total daily dose or cumulative dose of Exubera. Overall, in terms of pulmonary function, there is a small difference but it is not in magnitude, it does not progress over 2 years, and it is reversible 6 weeks after discontinuation.

It is recommended that all patients should have spirometry (FEV1) assessed prior to initiating therapy with Exubera; assessment of DL_{CO} should be considered. Use of Exubera is not recommended in patients with baseline FEV1 or DL_{CO} <70% predicted. However, efficacy and safety in this population have not been established.

In follow-up pulmonary assessment, spirometry (FEV1) is recommended 6 months after initiation and annually thereafter even in the absence of pulmonary symptoms. In patients who have a decline of ≥20% in FEV1 from baseline, PFTs should be repeated. If the ≥20% decline from baseline FEV1 is confirmed, Exubera should be

discontinued. The presence of pulmonary symptoms and lesser declines in pulmonary function may require more frequent monitoring of pulmonary function and consideration of discontinuation of Exubera.

Conclusion: Promises and Concerns

Although the products available today show promise, there are still significant challenges ahead. To date, we still need better comparator studies. We need to see better HbA1c levels, as all of the current studies have shown 7.0–7.5%, which is not enough. We further need to see a better control group with pens, with continuous subcutaneous insulin infusion systems, and with analogs. Finally, we need to have longer term safety data (>2 years).

Another concern is the cost. The success of these sytems will depend on its affordability. The cost in California is $150 for the equivalent of a 10-milliliter regular insulin vial, which usually costs $30, $40, or $50. In addition, the initial price of the device is about $800. Cost could be a considerable obstacle in the widespread acceptance and use of inhaled insulin systems.