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Inhaled human insulin: An inspiration for patients with diabetes mellitus?

■ ABSTRACT

Inhaled insulin offers a novel option for controlling blood glucose levels in type 1 and type 2 diabetes, obviating the need for multiple daily injections. The first of several delivery systems, insulin Exubera, was recently approved by the US Food and Drug Administration (FDA). However, questions remain regarding its efficacy, cost-effectiveness, and possible deleterious effects on pulmonary function. This review will discuss the pharmacology, efficacy, important clinical trials, and practical aspects of inhaled insulin, and potential concerns associated with its use.

■ KEY POINTS

All of the inhaled insulins currently under development are for prandial coverage only; patients still need subcutaneous injections of long-acting insulins for basal coverage.

Dosing will likely be highly individualized, as bioavailability varies among individuals.

Small declines in pulmonary function were seen in trials of insulin Exubera. Although these were not clinically significant, the FDA recommends pulmonary function testing at the start of Exubera therapy, at 6 months, and every year thereafter. Exubera is contraindicated in patients with preexisting lung disease.

In clinical trials, hemoglobin A_{1c} levels fell at least as much with inhaled insulin as with subcutaneous insulin injections, and the incidence of hypoglycemic episodes was similar with both regimens.

IN JANUARY 2006, the US Food and Drug Administration (FDA) approved insulin Exubera for the treatment of diabetes mellitus. Exubera is the first nonsubcutaneous form of insulin to reach this milestone, but several other forms of inhaled insulin are also undergoing clinical testing.

See related editorial, page 580

Since Banting and Best first isolated insulin in 1922, the subcutaneous route has remained the only option for taking it on a long-term basis, although progress has been made in its delivery (eg, via insulin pumps) and formulation (eg, long-acting insulins and insulin analogues).

Large studies have shown that in patients with either type 1 or type 2 diabetes, tighter glycemic control leads to reduction in microvascular complications.^{1,2} However, many patients fail to adhere to their regimens, particularly if they need to give themselves injections.^{3,4}

In response to these issues, a number of alternative routes of insulin delivery have been investigated, including oral, buccal, nasal, and dermal. Most of these have met with little success, owing to pharmacokinetic limitations, absorption problems, and instability of the formulations.

Pulmonary delivery of insulin has been more promising. As early as 1971, Wigley et al⁵ showed that regular insulin, given as an aerosol via a nebulizer, lowered blood glucose levels in rabbits and in healthy human volun-

TABLE 1

Inhaled insulin preparations under development

NAME	FORM OF INSULIN	SIZE OF PARTICLE (MICRONS)	ONSET OF ACTION (MINUTES)	TIME TO PEAK (MINUTES)	DURATION OF ACTION (HOURS)	MAKER
Exubera*	Dry powder	3	7	60	4–6	Pfizer, Necktar
AIR	Dry powder	10–20	15	30–45	3–5	Eli Lilly, Alkermes
Technosphere	Dry powder	2–5	5	39	3–4	MannKind
AERx iDMS	Aerosol liquid	2–3	5	49–65	4–6	Novo-Nordisk

*Approved by the US Food and Drug Administration; all others are undergoing phase III trials

teers. Later, Laube et al^{6,7} showed that nebulized porcine insulin lowered blood glucose levels in patients with type 2 diabetes. Since then, a number of inhaled insulin formulations have been studied, and insulin Exubera should soon be available for patients.

■ GETTING THE INSULIN DEEP INTO THE LUNGS

In theory, inhalation is a good way to get therapeutic peptides such as exogenous insulin into the systemic circulation. Some advantages of using this route include the large surface area of the alveoli—50 to 150 m²—which is perfused by approximately 5 liters of blood per minute.⁸ In addition, the membrane separating the alveolar space from the blood is less than 1 μm thick. Therapeutic peptides can cross this thin membrane rapidly without being exposed for very long to any peptidases that could break them down. In any event, these enzymes are present in far fewer numbers and concentrations in the lungs than in the gastrointestinal tract.

But first the drug has to *reach* the alveoli, which is a challenge (FIGURE 1). In contrast, inhaled asthma drugs do not have to go as deep, because they act locally on the airway.

Nebulizers can get insulin deep enough into the lungs but they exert high shearing forces on the particles, leading to denaturation of peptides. Because of this concern, inhaled human insulin systems that have progressed

through safety and efficacy trials so far do not use a nebulizer: they use dry powders and liquid aerosols instead. Of the two, dry powders deliver more drug per inhalation, are more chemically stable at room temperature, and have superior resistance to bacterial growth.⁹

Particle size and density play an important role in determining how far a drug is delivered into the lungs and how fast it is absorbed. Generally, particles larger than 2 μm are more likely to be deposited in the oropharynx or proximal bronchial tree instead of reaching the distal alveoli. However, larger particles can still be delivered consistently to the alveoli if they are porous and less dense.¹⁰ Most inhaled human insulin products in development utilize particles between 1 and 5 μm in diameter.

■ BIOAVAILABILITY IS LESS THAN WITH INJECTED INSULIN

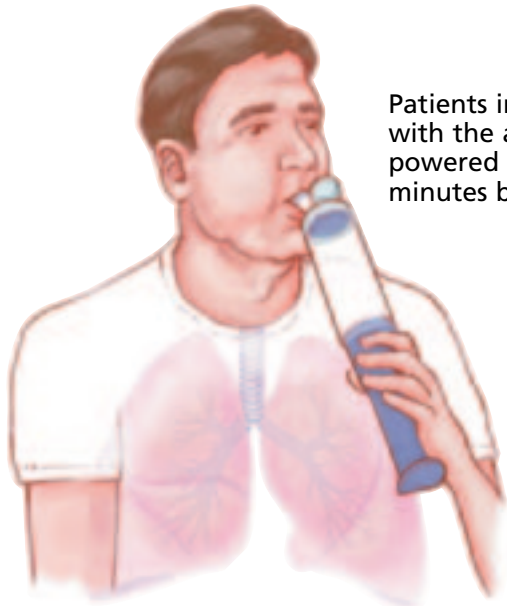
TABLE 1 lists the inhaled insulins currently under development. Each utilizes a unique inhalation device.

With each of the inhaled insulin systems, the bioavailability is approximately 10% to 20% that of a subcutaneous dose. This is due to loss of insulin by several mechanisms including adherence to the delivery device, deposition in the oropharynx and upper bronchial tree, exhalation of particles, breakdown by enzymes, and elimination by macrophages. The bioavailability may vary among the insulin systems, among patients, and even from dose to dose in the same patient.^{11–18}

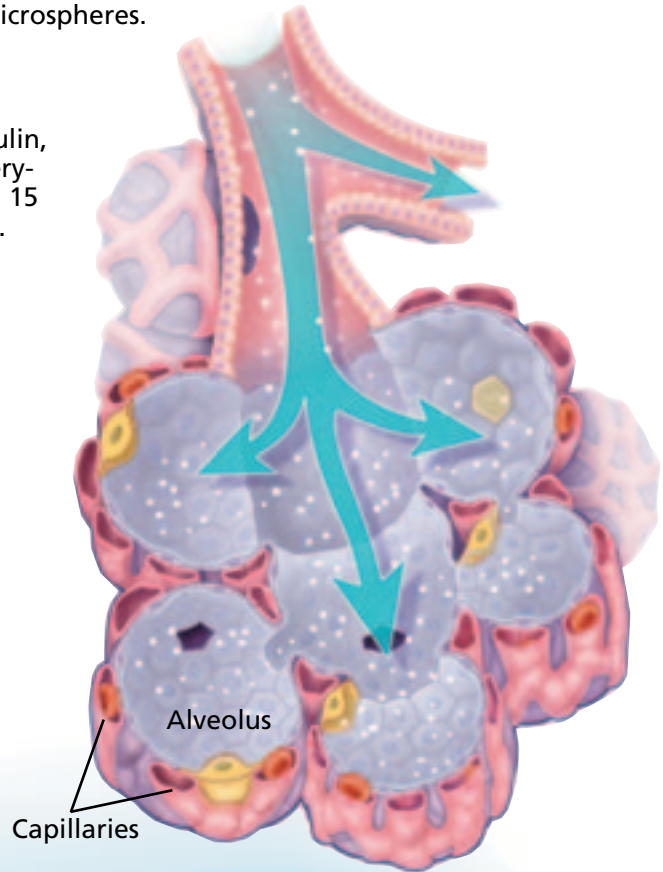
Absorption of inhaled insulin varies among patients

How inhaled insulin is delivered and absorbed

Exubera, the first inhaled insulin to be approved and marketed, consists of insulin as a dry powder, with particle sizes of about 3 microns. Other products under development use liquid aerosols or insulin contained within microspheres.



Patients inhale the insulin, with the aid of a battery-powered inhaler, 10 to 15 minutes before a meal.



Because much of the inhaled insulin powder is deposited in the inhaler device, oropharynx, and upper bronchial tree or is degraded by peptidases and removed by macrophages in the alveoli, only about 10% of the inhaled dose actually reaches the bloodstream.

The particles of insulin are encapsulated in vesicles, within which they cross the alveolar membranes. They then cross into the capillary.

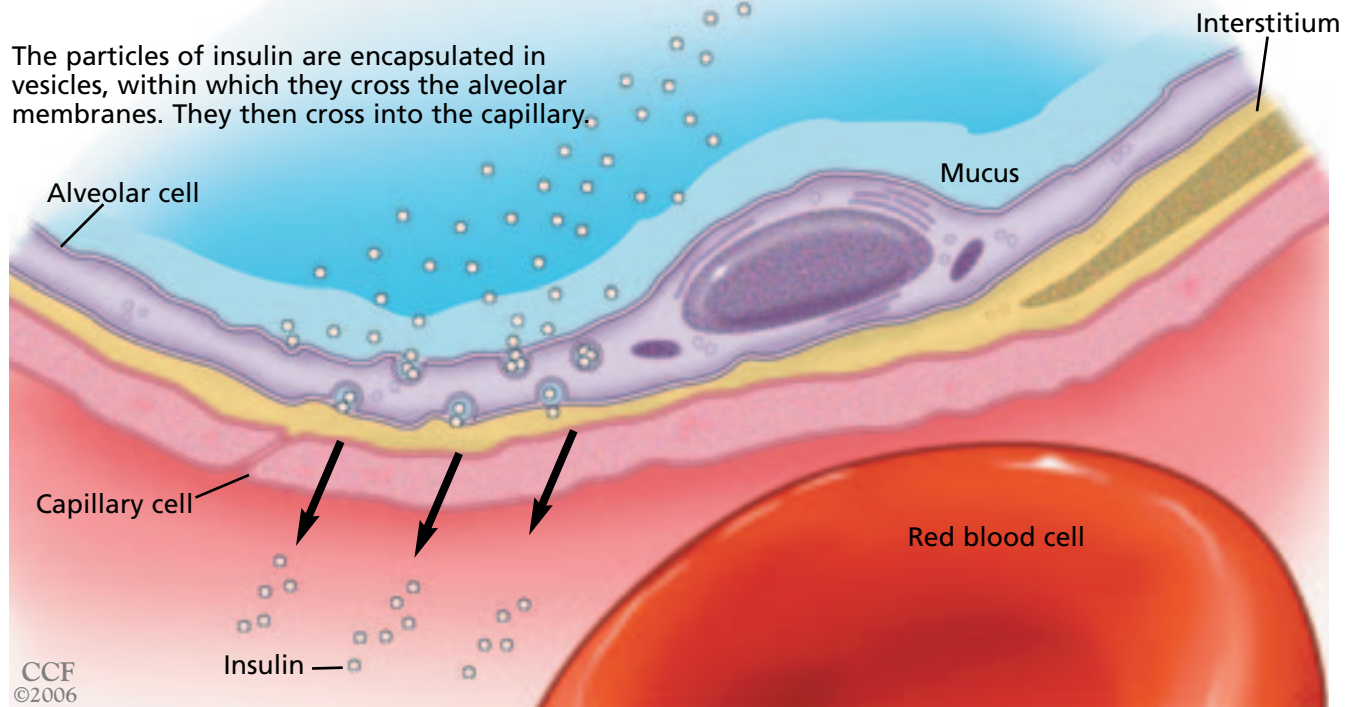


FIGURE 1

Medical Illustrator: David Schumick

Time-action profile of inhaled vs subcutaneous insulin

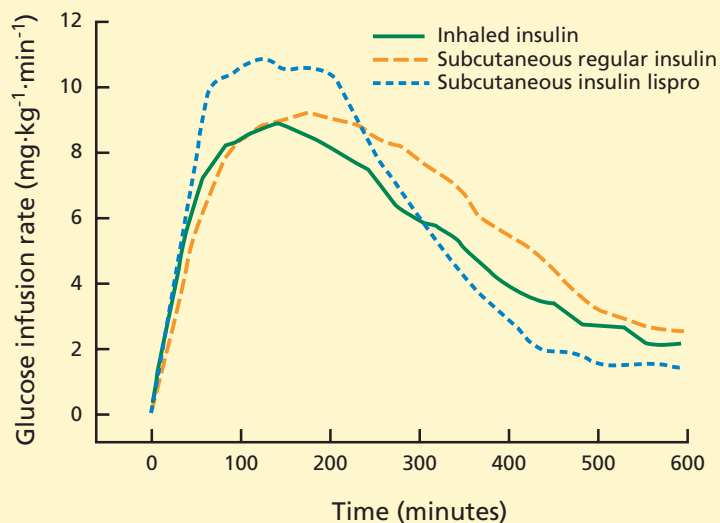


FIGURE 2. Time-action profiles after inhalation of insulin Exubera 6 mg, subcutaneous injection of insulin lispro 18 units, or subcutaneous injection of regular insulin 18 units. Data represent minute-by-minute glucose infusion rates necessary to keep blood glucose constant at 90 mg/dL for 600 min after administration of insulin in 17 healthy volunteers.

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FROM RAVE K, BOTT S, HEINEMANN L, ET AL. TIME-ACTION PROFILE OF INHALED INSULIN IN
COMPARISON WITH SUBCUTANEOUSLY INJECTED INSULIN LISPRO AND REGULAR HUMAN
INSULIN. DIABETES CARE 2005; 28:1077-1082.
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In a trial in healthy nonsmoking adults, an early form of inhaled human insulin was absorbed faster than subcutaneous regular insulin.¹⁵ Compared with insulin lispro, inhaled human insulin reached its maximum concentration in a similar time, but its onset of action was faster and its duration of action was slightly longer (FIGURE 2).¹⁹

Other dry-powder insulin preparations delivered by the Spiros and AIR systems performed similarly to those in the above study when compared with regular human insulin and insulin lispro in separate trials of similar design.^{13,14}

AERx, a liquid aerosol system, had an effect similar to that of the dry powder preparations.²⁰

The addition of an absorption enhancer on the inhaler device has also shown promise in

minimizing the variability of particle size and time to onset of action of inhaled human insulin.²¹

■ USING INHALED INSULIN

All inhaled insulin preparations developed thus far are designed to be used in the place of subcutaneous injections of rapid-acting insulin preparations with meals. In clinical trials, the dose was inhaled 10 to 15 minutes before the meal.

Thus far, no long-acting inhaled insulin systems have been developed. Most patients who use inhaled insulin will still need to take one or two injections per day of a long-acting insulin. Therefore, conversion of subcutaneous regimens to inhaled regimens involves only the prandial doses.

Insulin Exubera will come in 1-mg and 3-mg blister packs. The 1-mg pack is approximately equivalent to 3 units of subcutaneously injected insulin, and the 3-mg pack is approximately equivalent to 8 units. These numbers serve as an initial guide, but adjustments will likely need to be made on an individual basis because of the inherent interindividual variability in absorption (TABLE 2).

There is also a weight-based dosing scheme, which also has limitations because it does not take insulin sensitivity into account.²²

Caveats

There are a number of important caveats to note in the practical use of inhaled human insulin.

Most important is that inhaled insulin is contraindicated in patients with any degree of pulmonary compromise. This implies that before starting this therapy, providers should obtain baseline spirometry testing to rule out the presence of occult pulmonary disease.

In addition, active smokers should not be started on inhaled insulin, and previous smokers must demonstrate at least 6 months of abstinence from tobacco. The impact of "second-hand smoke" is unclear, but physicians should exercise caution in patients exposed to second-hand smoke due to the possibility of absorption variability.

Following initiation of inhaled insulin

**TABLE 2**

How to use insulin Exubera

Who may take it

Approved for use in both type 1 and 2 diabetes mellitus

Who should not take it

Contraindicated in patients with chronic pulmonary diseases (ie, asthma, chronic obstructive pulmonary disease, and interstitial lung disease)

Contraindicated in smokers (and in those who quit < 6 months before starting therapy)

The significance of passive smoke exposure is unclear

When to take it

Before meals

How much to take

Weight-based: 1 mg for patients weighing 30.0–39.9 kg, and then add 1 mg for every 20 kg > 40 kg.

Conversion from an established subcutaneous insulin regimen: 1-mg blister pack equals approximately 3 units subcutaneously injected insulin; 3-mg blister pack equals approximately 8 units subcutaneously injected insulin

Important note: Three 1-mg blister packs produce serum insulin levels greater than that with one 3-mg blister pack

How to monitor for potential adverse effects

Baseline spirometry is recommended for all patients

Repeat spirometry is recommended for all patients after 6 months of therapy

Spirometry should be performed annually thereafter, even in the absence of pulmonary symptoms

In patients who have a decline of $\geq 20\%$ in forced expiratory volume in 1 second from baseline, pulmonary function tests should be repeated for confirmation

If the $\geq 20\%$ decline from baseline forced expiratory volume in 1 second is confirmed, then insulin Exubera should be discontinued

How much will it cost?

Unclear at this time; however, anticipated to be higher than subcutaneous insulin therapy

therapy, repeat spirometry is recommended in all patients at 6 months regardless of the presence or absence of pulmonary symptoms. Thereafter, spirometry should be performed yearly as long as there is no deterioration of pulmonary function. In patients in whom a decline of more than 20% in forced expiratory volume in 1 second (FEV_1) is noted, spirometry should be repeated to confirm the findings, and if confirmed, inhaled insulin should be discontinued and the patient's pulmonary function followed closely.

Another potential concern for physicians and patients is whether dosing alteration is required if an upper respiratory tract infection develops. Although limited data and observations indicate no need to change dosing of inhaled human insulin in that setting, we strongly recommend very close monitoring of glycemia during upper respiratory tract infections in order to detect any changes in insulin absorption that may occur.

■ STUDIES OF INHALED INSULIN

Studies in type 1 diabetes mellitus

Quattrin et al²³ randomized 355 patients to receive either conventional treatment (regular human insulin subcutaneously before meals plus neutral protamine Hagedorn [NPH] insulin subcutaneously twice daily) or insulin Exubera before meals plus ultralente insulin subcutaneously every night. At baseline, the hemoglobin A_{1c} level was 8.1% in both groups; at 6 months it was 7.9% in the insulin Exubera group and 7.7% in the conventional treatment group.

Skyler et al²⁴ randomized 328 patients with type 1 diabetes to take either insulin Exubera or regular insulin before meals. Both groups also received NPH insulin before breakfast and at night. At 6 months, glycemic control in the two groups was similar, but patients taking the inhaled insulin had a lower incidence of hypoglycemia.

Comment. In both of these trials, inhaled

Effect of inhaled insulin on hemoglobin A_{1c} in clinical trials

Studies in type 1 diabetes

- Skyler et al³⁷
Inhaled insulin plus ultralente
Subcutaneous injections
- Quattrin et al²³
Insulin Exubera plus ultralente
Regular insulin plus NPH
- Skyler et al²⁴
Insulin Exubera plus NPH
Regular insulin plus NPH

Studies in type 2 diabetes

- Weiss et al³⁸
Inhaled insulin plus oral agents
Oral agents alone
- Hollander et al¹⁶
Insulin Exubera plus ultralente
NPH plus regular (70/30)
- DeFronzo et al²⁸
Insulin Exubera alone
Rosiglitazone alone
- Hermansen et al²⁶
Insulin AERx plus NPH
Regular insulin plus NPH

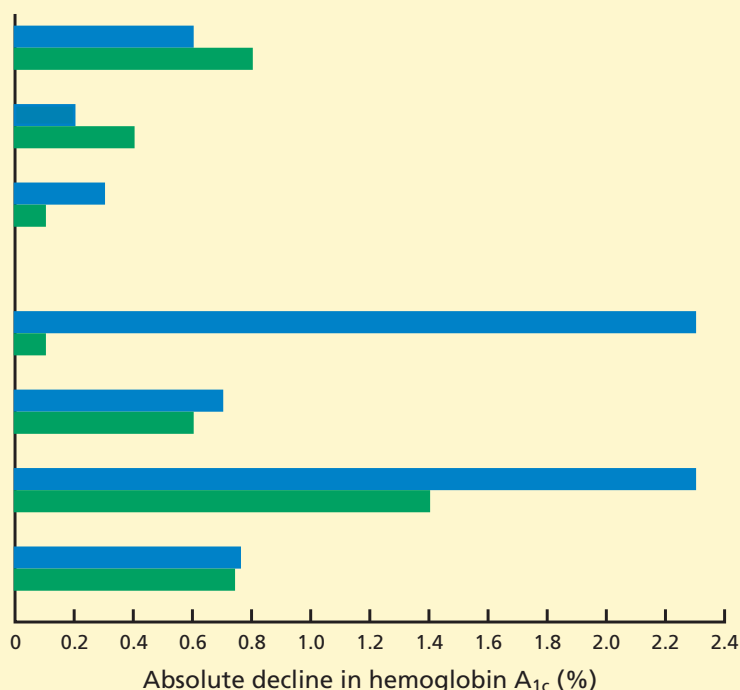


FIGURE 3

Studies of inhaled insulin vs lispro, aspart, or glulisine have yet to be published

insulin was equal or superior to regular insulin in lowering hemoglobin A_{1c} levels (FIGURE 3) without excessive risk of hypoglycemia (FIGURE 4). Long-term trials comparing inhaled human insulin and rapid-acting insulin analogues (insulins lispro, aspart, and glulisine) have yet to be published.

Studies in type 2 diabetes mellitus

Cefalu et al²⁵ first reported the extended use of inhaled human insulin in 26 obese patients with type 2 diabetes in 2001. The patients were on stable insulin regimens and were not taking oral hypoglycemic agents. They were randomized to either continue their conventional two to three subcutaneous injections per day or start inhaled human insulin with a single nighttime ultralente dose. Inhaled human insulin significantly improved hemoglobin A_{1c} over the course of the trial.

Hollander et al¹⁶ compared two regimens in 298 overweight patients with type 2 diabetes: insulin Exubera with meals plus bedtime ultralente vs twice-daily doses of NPH and

regular insulin in a premixed ratio of 70:30 (70/30 insulin). At the end of 6 months, the decrease in mean hemoglobin A_{1c} was similar in both groups. However, the insulin Exubera group had fewer episodes of hypoglycemia and more patients reaching a hemoglobin A_{1c} level of less than 7.0%.

Hermansen et al²⁶ enrolled 107 patients with type 2 diabetes in a 12-week trial of intensive therapy with the AERx insulin delivery system, which uses a liquid aerosol. Patients were randomized to receive either prandial insulin AERx or prandial subcutaneous regular insulin, both combined with bedtime NPH. Both groups achieved similar hemoglobin A_{1c} levels, but the AERx group had less hypoglycemia and lower fasting plasma glucose levels.

Rosenstock et al²⁷ randomized 309 patients who were taking two oral agents and had hemoglobin A_{1c} ranging between 8% and 11% to either add insulin Exubera to their regimen, continue their regimen unchanged, or stop their current regimen and take Exubera as monotherapy. The mean hemoglobin A_{1c}



Incidence of episodes of hypoglycemia in studies of inhaled insulin

Studies in type 1 diabetes

Skyler et al³⁷

Inhaled insulin plus ultralente
Subcutaneous injections

Quattrin et al²³

Insulin Exubera plus ultralente
Regular insulin plus NPH

Skyler et al²⁴

Insulin Exubera plus NPH
Regular insulin plus NPH

Studies in type 2 diabetes

Weiss et al³⁸

Inhaled insulin plus oral agents
Oral agents alone

Hollander et al¹⁶

Insulin Exubera plus ultralente
NPH plus regular insulin (70/30)

DeFronzo et al²⁸

Insulin Exubera alone
Rosiglitazone alone

Hermansen et al²⁶

Insulin AERx plus NPH
Regular insulin plus NPH

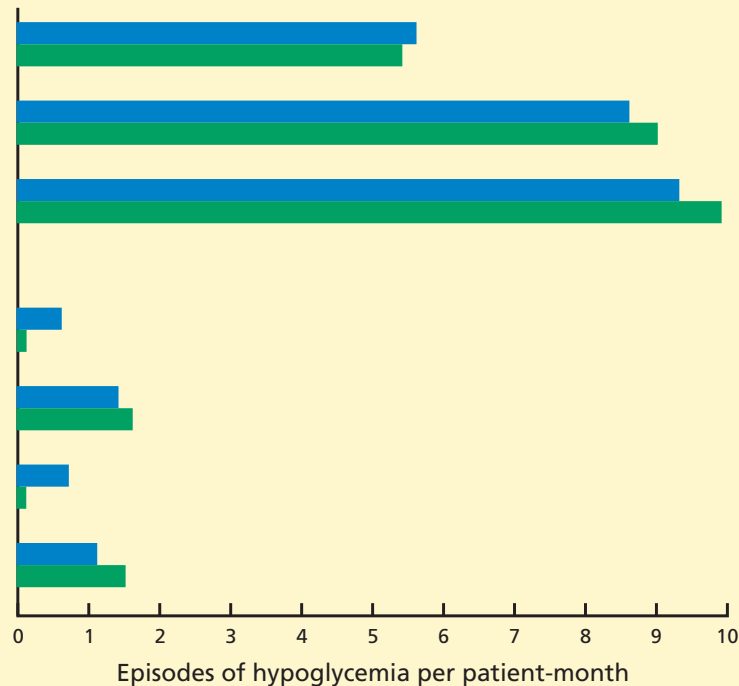


FIGURE 4

level in the Exubera-plus-oral-therapy group was 9.2% at baseline and dropped to 7.3% at 12 weeks. Compared with the group who continued on oral agents alone, the adjusted mean absolute drop in hemoglobin A_{1c} was 1.67% in the Exubera-plus-oral-agents group and 1.18% in the Exubera monotherapy group ($P < .001$ for both). A hemoglobin A_{1c} level lower than 7% was achieved in 32% of patients in the Exubera-plus-oral-agents group, 17% of patients in the Exubera monotherapy group, and only 1% of patients who were continued on oral agents alone.

DeFronzo et al²⁸ compared insulin Exubera and rosiglitazone as initial monotherapy in patients with untreated type 2 diabetes. The groups began the trial with similar hemoglobin A_{1c} values (9.5% and 9.4%, respectively). After 3 months of treatment, hemoglobin A_{1c} values had dropped significantly in both groups. However, 44% of the insulin Exubera group reached hemoglobin A_{1c} values less than 7.0% without significant hypoglycemia, compared with 18% of the rosiglitazone group.

Studies in special settings

Differences in age, sex, race, and body weight do not appear to influence the pharmacokinetics or pharmacodynamics of inhaled human insulin—but smoking does (TABLE 3).

In smokers, the alveolar-capillary membrane is more permeable, making absorption of insulin more rapid.²⁹

In studies of inhaled insulin AERx³⁰ and insulin Exubera,³¹ the absorption of both agents was significantly greater in chronic smokers than in nonsmokers. Acute smoking attenuates this effect, perhaps due to reversible constriction of respiratory smooth muscle.³⁰ Absorption declines within a few days of smoking cessation.³¹

In very limited observations in patients exposed to second-hand smoke, bioavailability was 20% to 30% less than in control subjects.³²

Lung disease. In patients with asthma, the absorption and the hypoglycemic effect of insulin AERx were attenuated and the intra-subject variability in insulin levels was greater

Exubera is contraindicated in patients with pulmonary disease

TABLE 3

Effects of various pulmonary conditions on insulin Exubera absorption

Asthma

Absorption was reduced by 20%–30% compared with controls
After treatment with an inhaled bronchodilator, absorption returned to baseline in mild and moderate asthma

Chronic obstructive pulmonary disease

Absorption increased by approximately 50% compared with controls

Interstitial lung disease

No studies available

Chronic smoking

In chronic smokers the absorption of insulin Exubera was increased to varying degrees
Smoking cessation for 7 days led to a 50% attenuation of this effect

Acute smoking

Absorption was attenuated by acute smoking compared with chronic smoking

Passive smoke exposure

Absorption was reduced by 20%–30% compared with controls

than in healthy controls.³³ Of note, in small studies, the bioavailability of insulin Exubera was approximately 50% higher in patients with chronic obstructive pulmonary disease than in controls.³²

Respiratory tract infections. Insulin AERx was studied in patients who had an acute upper respiratory tract infection but were otherwise healthy.³⁴ There were no significant differences in absorption or bioavailability to suggest a need to adjust the dose during acute respiratory illnesses. No studies published to date have examined the impact of respiratory tract infections on insulin Exubera. As stated earlier, we recommend close monitoring while patients have upper respiratory tract infections.

■ SAFETY AND PATIENT FACTORS

Safety of inhaled insulin

Pulmonary changes observed in trials of insulin Exubera included a statistically significant decrease from baseline of the carbon monoxide diffusion capacity (DLCO) and FEV₁ in patients with type 1 diabetes treated for 6 months.^{23,24} However, this is not believed to represent a clinically significant

change in pulmonary function. Additionally, no changes were seen in patients with type 2 diabetes in a trial with a similar design.¹⁶ The incidence of cough was similar in patients treated with inhaled human insulin and subcutaneous regular insulin.

In view of the potential adverse pulmonary effects of inhaled human insulin, the FDA has recommended pulmonary function testing when starting insulin Exubera, repeated after 6 months, and then repeated yearly regardless of pulmonary symptoms.²² Exubera is contraindicated in patients with preexisting pulmonary disease.

Although in vitro studies have shown that insulin promotes growth, inhibits apoptosis, and enhances proliferation of airway smooth muscle and bronchial epithelium,^{35,36} the clinical consequence of these actions is uncertain. So far, there have been no reports of pulmonary fibrosis or other adverse outcomes in studies in animals or humans.

Hypoglycemia is a potential concern with any insulin preparation. In long-term trials in both type 1 and type 2 diabetes, little difference in the overall incidence of hypoglycemic episodes was noted between inhaled human insulin and subcutaneous regular insulin.

In type 1 diabetes, the frequency of all hypoglycemic episodes with insulin Exubera was the same as with subcutaneous regular insulin over 12 and 24 weeks of therapy (FIGURE 4).^{23,37} However, in a 6-month trial in patients with type 1 diabetes, severe hypoglycemia was twice as frequent with insulin Exubera compared with subcutaneous regular insulin.²⁴

In type 2 diabetes, the incidence of hypoglycemia observed with the use of insulin Exubera and AERx was similar to that observed with subcutaneous regular insulin (FIGURE 4).^{16,26} On the other hand, the incidence of hypoglycemia was predictably higher with insulin Exubera than with oral hypoglycemic agents.^{28,38}

Insulin-antibody binding has been observed in trials of inhaled human insulin. In phase II and III trials, the prevalence of insulin antibodies was significantly higher in patients using insulin Exubera than in those receiving subcutaneous insulin.^{16,23,24,28,38} Patients with type 1 diabetes had higher levels of antibodies than those with type 2 diabetes.



However, in a 24-month extension of the initial phase II and III trials of insulin Exubera, the presence of insulin antibodies had no correlation with hemoglobin A_{1c} level, change in insulin dose, or incidence of hypoglycemia in the short term or long term.³⁹ There was also no correlation between antibodies and changes in pulmonary function or hypersensitivity reactions. A pharmacodynamic study demonstrated no impact of insulin-binding antibodies on the time-action profile of inhaled human insulin or postprandial glucose tolerance.⁴⁰ Therefore, the presence of insulin-binding antibodies appears to have no adverse clinical consequences.

Inhaled insulin will probably cost more

As outlined above, the bioavailability of inhaled human insulin is approximately 10% that of subcutaneous insulin. While precise dosing information for each insulin delivery system is not yet available, it is clear that patients will require considerably more inhaled insulin than subcutaneous insulin to maintain equivalent glycemic control. Thus, inhaled human insulin will likely cost more than subcutaneous preparations. Insurance coverage for inhaled insulin remains to be determined.

Patient acceptance and compliance

Patients prefer inhaled human insulin to subcutaneous insulin. Significantly more patients with type 1 diabetes using insulin Exubera said they were satisfied overall than did those using subcutaneous insulin (35.1% vs 10.6%, $P < .01$).⁴¹ Findings in patients with type 2 diabetes were similar.⁴²

Compliance with an insulin regimen was compared in patients with type 2 diabetes taking insulin AERx or subcutaneous insulin in a 12-week trial.⁴³ Adherence to the AERx regimen was 94%; in contrast, adherence to subcutaneous insulin regimens was 64%.³ Furthermore, in another trial, when patients with type 2 diabetes were offered a choice of continuing their conventional regimen (oral

hypoglycemic agents or diet) or starting a regimen with insulin, those offered Exubera were more likely to accept insulin rather than stay with a failing regimen.⁴⁴

CONCLUSIONS

In the coming months, inhaled human insulin will offer patients and physicians another option for treatment of diabetes. Inhaled insulin seems to offer an alternative to preprandial subcutaneous injection of insulin with reliable and predictable dose-response curves. Advantages include freedom from multiple daily injections (although most patients will still require an injection of a long-acting insulin for basal coverage), better patient adherence, and greater flexibility for insulin dosing. Potential disadvantages include the possibility of long-term changes in pulmonary vasculature and architecture, the unknown long-term significance of insulin antibody formation, and higher cost. Longer-term studies and observations are necessary to further study these issues.

The presence of any preexisting pulmonary disease is a contraindication for the use of insulin Exubera because of the paucity of knowledge regarding the long-term pulmonary effects of inhaled human insulin, especially in those with compromised pulmonary function.

Overall, inhaled human insulin represents an exciting new chapter in the management of diabetes and is likely to become an important tool in the management of both types 1 and 2 diabetes. However, due to the unclear long-term safety of inhaled human insulin, patients and physicians should carefully assess their options prior to embarking upon its use in the routine management of diabetes mellitus.

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Patients prefer inhaled insulin over injections

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