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Inhaled Human [rDNA Origin] Insulin, a Novel Formulation for Diabetes Mellitus

David Q. Pham, PharmD, Henry Cohen, PharmD, FCCM, and Valery Chu, PharmD

Diabetic complications have been reduced significantly with the introduction of insulin more than 8 decades prior. Despite the proven benefits of normal glycemic levels, patients are deterred by the inconvenience and expect worse pain than there is on average with multiple daily insulin injections. Inhaled insulin was approved by the Food and Drug Administration in early 2006 and is a novel product that introduces inhaled insulin as an alternate to the traditional subcutaneous delivery system, and

hence could potentially improve patient compliance. The objective of this article is to review the clinical pharmacology, pharmacokinetic and pharmacodynamic properties, clinical efficacy, and tolerability of inhaled insulin.

Keywords: Inhaled insulin; Exubera; clinical trials; efficacy; adverse effects

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The long-term complications associated with diabetes mellitus include nephropathy, retinopathy, neuropathy, cardiovascular disease, peripheral vascular disease, and cerebrovascular disease.¹ These complications are influenced not only by the duration of the disease but also by the average level of chronic hyperglycemia, which is most reliably measured with the glycosylated hemoglobin assay (A1C).² To successfully reduce A1C, patients must achieve preprandial and postprandial plasma glucose goals. A reduced A1C is associated with a decline in diabetic complications in type 1 diabetic patients, as demonstrated in the Diabetes Control and Complications Trial (DCCT),³ and type 2 diabetic patients, as demonstrated in the UK Prospective Diabetes Study (UKPDS).⁴ Hence, novel medications that have the potential to reduce A1C are studied extensively.

In type 1 diabetes, insulin therapy is the foundation of management. The DCCT, along with many

other studies, revealed that effective normalization of plasma glucose requires up to 5 injections daily.^{3,5-7} Injections of long- and intermediate-acting insulin once (eg, glargine) to twice (eg, neutral protamine hagedorn [NPH]) daily in conjunction with 2-3 rapid-acting injections (eg, regular or lispro) administered prandially are the mainstays of therapy for the majority of patients with type 1 diabetes. Even the recent approvals of the glucagon-like peptide-1 receptor agonist (ie, exenatide) and the synthetic analog of amylin (ie, pramlintide) require injections 2 and 3 times daily, respectively. Despite the proven benefits of normal glycemic levels, patients are deterred by inconvenience and expect worse pain than there is on average with multiple daily injections.

In type 2 diabetes, insulin injections may be deferred initially but are inevitable for most. The traditional management of type 2 diabetes involves the initiation of oral antidiabetic agents. The oral agents available for use include the sulfonylureas, biguanide, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, and the newly approved dipeptidyl peptidase-4 inhibitor (ie, sitagliptin). However, as time progresses and insulin secretory capacity becomes insufficient, adequate treatment goals become increasingly arduous to achieve.⁸ Subsequently, the doses of the oral antidiabetic agents are maximized, and multiple agents with different mechanisms of action are added, increasing the risk of adverse effects, hypoglycemia, and drug-drug interactions. Furthermore, of

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the oral antidiabetic medications, all have common relative or absolute contraindications—such as poor renal or hepatic function or heart failure with metformin use, heart failure with thiazolidinedione use, irritable bowel disease or poor renal function with alpha-glucosidase inhibitors, drug interactions with meglitinides, and sulfonamide allergy with sulfonylurea use.⁹ In fact, a study of the UKPDS indicated that sulfonylureas and metformin appear to have a limited duration of effectiveness after 5 years of therapy.^{4,10} To continue reducing the risk for diabetic complications, these patients must then achieve control using insulin therapy.¹¹ Although insulin therapy has not traditionally been introduced early in the course of type 2 diabetes, early initiation has been confirmed to reducing diabetic complications.¹² Although type 2 diabetes can be diagnosed at any time of life, it is usually seen in the fourth decade of life—in a population that is increasingly becoming elderly with greater longevity.

In both type 1 and 2 diabetes, the American Diabetes Association (ADA) defines glycemic control by achieving A1C of <7%, preprandial capillary plasma glucose between 90 and 130 mg/dL, and peak postprandial capillary plasma glucose of <180 mg/dL.¹³ Particularly in type 1 diabetes, the ADA recommends that more stringent glycemic goals of A1C <6% may further reduce complications at the risk of increased hypoglycemia, but the absolute risks and benefits of lower targets are unknown.¹³

The management of diabetes has been revolutionized by insulin therapy for the past 8 decades. However, even with the advances made and millions of lives saved, patients are still unable to achieve long-term euglycemia. Patients suffering from diabetes mellitus often have difficulty with self-administration of insulin due to a decrease in manual and physical dexterity resulting from the development of neuropathy and visual difficulty resulting from the development of retinopathy. Although factors such as motivation, education, and socioeconomic status certainly affect the ability to achieve target glycemic control, the greatest physical barrier seems to be patients' and physicians' hesitation with adverse effects and resistance to the use of the most common route of insulin administration, subcutaneous injection.¹⁴⁻¹⁷

There is currently one inhaled insulin preparation approved for use in the United States. Inhaled insulin provides a rapid-acting, orally inhaled insulin delivery system that may be more convenient to patients than the traditional subcutaneous delivery systems. The potential of improved compliance and better diabetic control for patients unable or unwilling to self-inject may be significant.

PHARMACOLOGY

The lungs, due to their highly vascular and easily permeable mucosal tissue beds, provide a superior absorption site for inhaled insulin action.¹⁸ Inhaled insulin is absorbed initially from the alveolar capillary endothelium cells and then released into the alveolar capillary bloodstream for absorption.¹⁹ With all orally inhaled medicinals, optimal systemic absorption of particles occurs between 1.5 and 2.5 μm . Particles <1 μm are exhaled and particles >5 μm are primarily lodged in the tracheobronchial and oropharyngeal zone, which produces no medication effect.²⁰ Inhaled insulin delivery technology enables particles to be within the range of 1 to 5 μm . However, due to the limited amount of inhaled insulin that is within the absorbable particle size range, only 6% to 10% of inhaled insulin is absorbed into the systemic circulation.¹⁹

Pharmacokinetics

Pulmonary delivery of insulin has been the most promising of the alternative methods of administration explored. Several inhalation insulin delivery systems are presently under development, varying by dosage form (powder vs liquid), inhalation device, and particle size—hence, their pharmacokinetic profiles and physiologic responses will likewise be variable and should not be assumed to be similar.¹¹

Inhaled insulin is a dry-powder inhaler, formulated to target insulin delivery for a prandial glycemic effect. The assumed relative bioefficacy of inhaled insulin compared to regular and lispro insulins was 10% and 11%, respectively—this was derived from unpublished pharmacokinetic data that demonstrated that 1 mg of inhaled insulin delivers approximately 3 units of subcutaneous insulin (data on file).²¹

Rave et al²² conducted a randomized, open-label, crossover euglycemic clamp study in 18 healthy, non-smoking male volunteers using the inhaled insulin system to compare its time action profile with subcutaneous regular and lispro insulins. Inhaled insulin had the most rapid onset of action (as measured by time to early half-maximal effect) of 32 minutes as compared to 48 minutes for regular insulin ($P < .001$) and 41 minutes for lispro insulin ($P < .05$). Inhaled insulin and lispro insulin achieved peak effect comparably (143 vs 137 minutes, respectively, *ns*), whereas regular insulin took significantly longer (193 minutes, $P < .01$). Duration of action of inhaled insulin, however, was comparable to regular insulin (387 vs 415 minutes, respectively, *ns*) and longer than lispro insulin (313 minutes, $P < .01$). In clinical trials with type 1 and type

2 patients, inhaled insulin can be expected to affect postprandial hyperglycemia slightly faster than lispro insulin (within 10-20 vs 25 minutes), with a peak similar to lispro insulin (within 1 hour), and continue to exert an effect for as long as regular insulin (6 hours).²³

No relative differences in inhaled insulin's onset, peak, and duration of effect were noted in pediatric (<6 years) and geriatric patients (mean 72 years) or based on sex, race (Caucasians vs Japanese), body mass index (mean 33 kg/m²), or pregnancy.^{23,24} Similar to regular and lispro insulin, inhaled insulin dose reductions will be necessary in patients with renal and/or hepatic dysfunction, but no pharmacokinetic studies were performed in these populations.²³ Of importance, a study using three 1-mg blisters of inhaled insulin yielded a 30% to 40% higher C_{max} and AUC relative to one 3-mg blister.²³

In an unpublished pharmacokinetic trial evaluating inhaled insulin in nondiabetic patients with chronic obstructive pulmonary disease (COPD) (n = 24), there was a 2-fold increase in the systemic bioavailability relative to normal subjects without COPD.²³ In contrast, in an unpublished pharmacokinetic trial evaluating inhaled insulin in nondiabetic patients with mild asthma not receiving bronchodilator therapy, there was a 20% decrease in bioavailability relative to normal subjects without asthma.²³ Nevertheless, because safety and efficacy trials in patients with underlying pulmonary diseases have not been conducted, inhaled insulin is not recommended but not contraindicated in such patients.

DATA SOURCES

The safety and efficacy of inhaled insulin administration has been evaluated in a plethora of clinical trials. Using the search terms *inhaled insulin*, *Exubera*, and *clinical trials*, with limitations set to distinguish human subjects participating in clinical trials written in English that involved type 1 and 2 diabetes mellitus, several peer-reviewed articles were identified in MEDLINE (1966 to November 2006), EMBASE (1980 to November 2006), IPA (1970 to November 2006), and IDIS (1966 to November 2006). Only clinical trials that included A1C as a study endpoint are summarized in this review. No abstracts were reviewed.

For all trials reviewed, hypoglycemia was defined as characteristic symptoms without self-monitoring blood glucose (SMBG) measurement that promptly resolved with food intake, subcutaneous glucagon, or intravenous glucose; characteristic symptoms with SMBG <60 mg/dL; or any SMBG measurement <50 mg/dL with or without symptoms. Severe hypoglycemia was

defined as (1) requiring assistance by another, (2) involving neurological symptoms (eg, memory loss, confusion, irrational behavior, unusual difficulty walking, seizure, loss of consciousness), and (3) associated with an SMBG <50 mg/dL or, in the absence of an SMBG measurement, that was reversible with oral carbohydrate, subcutaneous glucagon, or intravenous glucose.

For the majority of trials reviewed, exclusion criteria included poorly controlled asthma or clinically significant COPD, smoking during the past 6 months, or significant pulmonary disease defined as carbon monoxide diffusing capacity of the lung (DL_{CO}) <75%, total lung capacity (TLC) <80% or >120%, and forced expiratory volume in 1 second (FEV₁) <70% predicted. Patients who were pregnant, lactating, or planned to be pregnant were also excluded. Hence inhaled insulin is not recommended in these patient populations.

REVIEW OF CLINICAL TRIALS FOR INHALED INSULIN IN TYPE 1 DIABETES MELLITUS

To date, 2 randomized, comparative phase III trials have been published studying inhaled insulin in patients with type 1 diabetes. Quattrin et al²⁵ set out to determine noninferiority of A1C control between a regimen combining preprandial inhaled insulin with a single bedtime injection of basal ultralente and a twice-daily preprandial regular insulin with twice-daily NPH. This 24-week, open-label, randomized, multicenter trial enrolled 335 patients with type 1 diabetes already taking a multiple injection insulin regimen prior to enrollment. Patients with significant pulmonary disease or smoking use were excluded.

After 24 weeks, the A1C change from baseline in each treatment group was less than 0.5%, which met the investigators' prespecified criteria for comparability (95% confidence interval [CI]: 0.01 to 0.32). The percentage of patients achieving an A1C <7% was 15.9% in the inhaled insulin group and 15.5% in the subcutaneous insulin group (adjusted odds ratio [OR]: 0.92; 95% CI: 0.40 to 2.10). Patients receiving inhaled insulin experienced median fasting plasma glucose reductions of 35 mg/dL as compared to 10 mg/dL for the subcutaneous insulin group (95% CI: -43.39 to 6.95). Median 2-hour postprandial glucose values were reduced by 30 mg/dL with inhaled insulin and increased by 1 mg/dL with subcutaneous insulin (95% CI: -54.6 to 6.0). The authors concluded noninferiority, claiming that mean short-acting and long-acting insulin doses remained comparable from baseline to the end of the study in both groups (exact doses of short- and long-acting insulin were not reported).

The risk of overall hypoglycemia was less in the group receiving inhaled insulin compared to the group receiving subcutaneous insulin (8.6 vs 9.0 events/subject month; risk ratio [RR]: 0.96; 95% CI: 0.93 to 0.99). Changes in weight were not assessed.

Fasting lipid panels were assessed at baseline and after 24 weeks. Although statistical analyses were not presented, the median changes from baseline in the group receiving inhaled insulin compared to the group receiving subcutaneous insulin were as follows: total cholesterol, 1 vs -5 mg/dL; high-density lipoprotein (HDL) cholesterol, -1.5 vs 1 mg/dL; low-density lipoprotein (LDL) cholesterol, 1 vs -6.5 mg/dL; and triglycerides, 12 vs 1 mg/dL, respectively. In summary, the inhaled insulin group appeared to have less favorable changes in the lipid parameters.

It is unclear why the 2 treatment groups were randomized to different types of basal insulin. Although the daily doses of ultralente and NPH insulins were similar between the groups, pharmacokinetic and pharmacodynamic responses to different types of insulins vary. This introduces an unnecessary variable in interpreting the results.

Skyler et al²⁴ conducted a similar 24-week, open-label, randomized, multicenter trial, enrolling 328 patients with type 1 diabetes already taking an insulin regimen prior to enrollment. History of significant pulmonary disorders and smoking use were excluded. Like Quattrin's group,²⁵ Skyler et al set out to determine noninferiority of glycemic control between preprandial inhaled insulin and preprandial regular insulin, but with all patients receiving twice-daily basal subcutaneous NPH insulin. After 24 weeks, the mean A1C reduction was 0.3% for the inhaled insulin group and 0.1% for the subcutaneous insulin group, compared to baseline (95% CI: -0.34 to 0.01). The percentage of patients achieving an A1C <7% was 23.3% with inhaled insulin and 22% with subcutaneous insulin (adjusted OR: 1.53; 95% CI: 0.75 to 3.14). Comparing fasting plasma glucose after 24 weeks, a mean reduction of 35 mg/dL was observed with inhaled insulin and a mean gain of 4 mg/dL with subcutaneous insulin (95% CI: -57.50 to 21.56). Two-hour postprandial glucose decreased in both groups, 21 mg/dL with inhaled insulin and 14 mg/dL with subcutaneous insulin (95% CI: -30.29 to 16.74). Mean short-acting insulin doses were 8.65, 6.95, and 10.43 units prebreakfast, prelunch, and presupper. Both short-acting and long-acting insulin doses were similar in all patients from baseline to end of study, with small increases in both groups by study end.

The overall hypoglycemia rate, reported in episodes per patient-month, was less in the group receiving

inhaled insulin than in the group receiving subcutaneous insulin (9.3 vs 9.9; risk ratio: 0.94; 95% CI: 0.91 to 0.97). Changes in weight were not assessed.

As with the earlier trial by Quattrin et al,²⁵ fasting lipid panels were assessed at baseline and after 24 weeks, with median changes presented, without statistical analyses. The median lipid changes from baseline in the group receiving inhaled insulin compared to the group receiving subcutaneous insulin were as follows: total cholesterol, -4 vs 5 mg/dL; HDL cholesterol, -4.5 vs 1 mg/dL; LDL cholesterol, -1.5 vs 3 mg/dL; and triglycerides, 6 vs 6 mg/dL, respectively.

PERSPECTIVES FOR TYPE 1 DIABETES MELLITUS CLINICAL TRIALS

Glycemic efficacy between inhaled insulin with a subcutaneous basal insulin and basal/bolus subcutaneous insulin regimens was found to be comparable in 662 treated type 1 diabetes patients in 2 phase III trials. Due to the nature of the delivery systems being compared, all trials were necessarily open-labeled. Both of the phase III trials in type 1 diabetes patients used similar study designs, patient populations, and exclusion and inclusion criteria. The major differences in the 2 trials were in the choice of basal subcutaneous insulin used by the inhaled insulin groups and the number of regular insulin injections used in the subcutaneous insulin groups. Considering that inhaled insulin has pharmacodynamic activity that overlaps both lispro and regular insulins, studies comparing inhaled insulin with lispro insulin as prandial coverage allow for balanced comparisons. The lipid parameter changes in the 2 trials are inconsistent and are of unknown significance. A summary of clinical trials for inhaled insulin in type 1 diabetes mellitus can be found in Table I.

REVIEW OF CLINICAL TRIALS FOR INHALED INSULIN IN TYPE 2 DIABETES MELLITUS

To date, 5 randomized, open label trials have been published studying inhaled insulin in patients with type 2 diabetes. Cefalu et al²¹ performed a randomized, 3-month, open-label trial to assess the safety and efficacy of inhaled insulin in type 2 diabetic patients who require insulin (n = 26). Included in the study were patients aged 35 to 65 years, weighing 100% to 175% of their ideal body weight, previously treated with a stable insulin regimen involving 2 to 3 injections daily for at least 1 month and with A1C 7% to 11.9%. Patients received 1 to 2 inhalations of inhaled insulin before each meal and ultralente insulin at bedtime.

Table I Summary of Clinical Trials for Inhaled Insulin in Type 1 Diabetes Mellitus

	Skyler et al ²⁴	Quattrin et al ²⁵
Study design	Randomized, open label, multicenter, comparative	Randomized, open label, multicenter, comparative
Length of study	6 months	6 months
Participants	Type 1 diabetes, n = 328	Type 1 diabetes, n = 335
Endpoints evaluated, inhaled insulin vs SC	Comparability of glycemic control (A1c), safety	Comparability of glycemic control (A1c), safety, satisfaction
Treatment	Inhaled insulin tid + Ultralente QHS vs regular/NPH insulin bid	Inhaled insulin tid + NPH insulin bid vs regular insulin tid + NPH insulin bid
Change in A1C, inhaled insulin vs SC	−0.4% vs −0.2% (adjusted difference −0.16%, 95% CI: −0.01 to 0.32)	−0.3% vs −0.1% (adjusted difference −0.16%, 95% CI: −0.34 to 0.01)
Hypoglycemic events, inhaled insulin vs SC		
Overall	9.3 vs 9.9 events/subject-month (RR: 0.94; 95% CI: 0.91 to 0.97)	8.6 vs 9.0 events/subject-month (7536 vs 7806 events) (RR: 0.96; 95% CI: 0.93 to 0.99)
Severe	6.5 vs 3.3 events/100 subject-months (RR: 2.00; 95% CI: 1.28 to 3.12)	5.5 vs 4.7 events/100 subject-months (RR: 1.16; 95% CI: 0.76 to 1.76)
Change in weight, inhaled insulin vs SC	+1.3 vs +1.5 kg (adjusted difference −0.19 kg; 95% CI: −0.91 to 0.53)	+0.9 vs +1.5 kg (<i>ns</i>)

bid, twice daily; tid, 3 times daily; QHS, at bedtime; A1C, glycosylated hemoglobin assay; NPH, neutral protamine hagedorn; SC, subcutaneous; CI, confidence interval; RR, risk ratio.

Inhaled insulin significantly reduced A1C by 0.71% ($8.67\% \pm 1.44\%$ at baseline to $7.96\% \pm 1.37\%$; 95% CI: -1.00% to -0.42%) at 3 months. Patients receiving inhaled insulin had no significant changes from baseline in postprandial glucose levels (240 ± 56 mg/dL at baseline vs 241 ± 57 mg/dL at end of study), 2-hour postprandial glucose levels (82 ± 53 mg/dL at baseline vs 70 ± 52 mg/dL at end of study), or weight gain (3-month change, -0.3 ± 2.9 kg; *P* not reported). There were no significant changes in spirometry (forced vital capacity [FVC], FEV₁, peak expiratory flow rate [PEF]), lung volume (TLC, functional residual capacity, residual volume), DL_{CO}, or oxygen saturation (by pulse oximetry; no values or *P* value reported). Mild to moderate hypoglycemic episodes were reported in 69% (*n* = 18) of patients receiving inhaled insulin, with an average of 0.83 episodes per month (*P* value not reported). No severe hypoglycemic episodes were reported. In total, there were 39 hypoglycemic episodes in the first 4 weeks and 22 episodes in the last 8 weeks of the study.

Major limitations of this trial included lack of a control group, lack of statistical analysis for most reported values, short treatment duration, small study population, and no recorded pulmonary function values. The authors conclude that type 2 diabetics who require insulin will benefit from the use of inhaled

insulin because of improved glycemic control with no adverse pulmonary effects.

DeFronzo et al²⁶ conducted an open-label, parallel-group, multicenter, 3-month randomized trial to evaluate whether premeal inhaled insulin (titrated to target glucose range of 80–140 mg/dL before meals and 100–160 mg/dL before bedtime) could achieve target blood glucose in type 2 diabetic patients failing therapy with diet and exercise compared to twice-daily rosiglitazone 4 mg (*n* = 145). In the inhaled insulin group, 44% achieved A1C <7% compared to 17.9% in the rosiglitazone group (adjusted OR: 4.43; 95% CI: 1.94 to 10.12). Changes from baseline in fasting plasma glucose and 2-hour postprandial glucose were not significant between the inhaled insulin and rosiglitazone groups. Mild to moderate hypoglycemic episodes were more common in the inhaled insulin group (a total of 153 episodes in 36 patients) than in the rosiglitazone group (9 episodes in 5 patients). The number of mild to moderate hypoglycemic episodes per subject month was 0.7 in the inhaled insulin group compared to 0.05 in the rosiglitazone group (RR: 14.72; 95% CI: 7.51 to 28.83). There was a nonsignificant increase in body weight in both the inhaled insulin group (1.9 kg) and the rosiglitazone group (0.8 kg; adjusted treatment group difference 0.95 kg; 95% CI: -0.18 to 2.09). Inhaled insulin did not exhibit any statistically significant

changes in pulmonary function tests compared with baseline for FEV₁ (−0.016 vs −0.001 L), FVC (0.002 vs 0.009 L), TLC (0.033 vs 0.064 L), and DL_{CO} (−0.973 vs −0.829 mL/[min × mm Hg]). Mild cough was reported more commonly in the inhaled insulin group (8%) than in the rosiglitazone group (1.5%). For both groups, insulin antibody binding was below the limit of quantitation (<3% binding). The authors concluded that in type 2 diabetic patients not controlled with diet and exercise, inhaled insulin may be more effective in improving glycemic control than rosiglitazone. Although the superiority of inhaled insulin over rosiglitazone was achieved by A1C reduction, using rosiglitazone as the comparative agent may have led to unjustified conclusions because rosiglitazone is not generally considered as the best first-line agent for monotherapy.²⁷⁻²⁹

Weiss et al³⁰ conducted an open-label, multicenter, parallel study to evaluate the safety and efficacy of inhaled insulin on glycemic control in type 2 diabetic patients inadequately controlled with sulfonylurea and/or metformin (n = 68). Patients were told to continue their oral antidiabetic agents regularly. Patients were randomized to receive either preprandial inhaled insulin or no inhaled insulin (control group).

After 3 months of therapy, the inhaled insulin group achieved a 2.3% reduction in A1C compared to 0.1% in the group receiving no inhaled insulin (95% CI: −2.7 to −1.7, *P* < .001). Fasting plasma glucose was reduced significantly from 227.48 ± 8.69 mg/dL at baseline to 172.36 ± 8.50 mg/dL in the inhaled insulin group compared with a reduction from 254.06 ± 11.54 mg/dL to 244.86 ± 9.16 mg/dL in the group receiving no inhaled insulin (95% CI: −80.64 to −40.73, *P* < .001). Hypoglycemia was more common in the inhaled insulin group, occurring 57 times compared to 6 events in the control group (RR: 10.7; 95% CI: 4.6 to 24.8, *P* < .001). There was no significant reduction in 2-hour postprandial glucose between the 2 groups (95% CI: −33.56 to 0.76, *P* = .06). Mean body weight was increased by 2.7 kg in patients receiving inhaled insulin versus 0.5 kg in the control group (95% CI: 1.3 to 3.7, *P* < .001). Although no statistics were employed, differences in FVC, FEV₁, TLC, and DL_{CO} were not observed.

The authors concluded that in type 2 diabetics failing to achieve adequate control with sulfonylurea and/or metformin, the addition of preprandial inhaled insulin to existing sulfonylurea and/or metformin improves glycemic control without the need for insulin injections.

Rosenstock et al⁸ performed a multicenter, open-label, randomized, controlled trial that assessed the

effect of inhaled insulin in type 2 diabetic patients (n = 309) failing oral antihyperglycemic therapy for at least 1 year who were stable with their oral regimen using 2 antidiabetic medications: an insulin secretagogue (a sulfonylurea or repaglinide) and an insulin sensitizer (a thiazolidinedione or metformin), with A1C between 8% and 11% and body mass index (BMI) <35 kg/m², over a 3-month study period. Patients received either preprandial inhaled insulin plus their existing stable regimen of 2 oral antihyperglycemic agents (n = 102) or preprandial inhaled insulin alone (n = 105), or they served as the control by remaining on their 2 oral antihyperglycemic agents only (n = 102). Doses of oral agents were unchanged throughout the duration of the study. Doses of inhaled insulin were titrated based on patients' self-monitored blood glucose testing.

After 3 months, a significant 1.9% reduction in mean A1C was found in the group receiving inhaled insulin with 2 oral antihyperglycemic agents and 1.4% in the group receiving inhaled insulin alone compared to 0.2% in the group receiving only oral therapy (*P* < .001). A significant percentage of patients achieving A1C <7% was also evident: 32% of patients in the inhaled insulin plus 2 oral agents group (adjusted OR: 44.7; 95% CI: 6.0 to 335.2) and 16.7% of patients in the inhaled insulin monotherapy group (adjusted OR: 19; 95% CI: 2.5 to 145.8) compared to 1% of patients in the 2 oral agents group. A significant reduction in fasting plasma glucose was reported compared to baseline: −53 mg/dL for patients in the inhaled insulin plus 2 oral agents group (adjusted treatment group difference, −53; 95% CI: −66 to −41) and −23 mg/dL for patients in the inhaled insulin monotherapy group (adjusted treatment group difference, −24; 95% CI: −36 to −11) compared to 1 mg/dL in the 2 oral agents group. Two-hour postprandial glucose also showed a significant reduction from baseline: −79 mg/dL for patients in the inhaled insulin plus 2 oral agents group (adjusted treatment group difference, −76; 95% CI: −93 to −58) and −66 mg/dL for patients in the inhaled insulin monotherapy group (adjusted treatment group difference, −62; 95% CI: −79 to −45) compared to −3 mg/dL in the 2 oral agents group.

Triglycerides were significantly reduced compared to baseline: −39 mg/dL for patients in the inhaled insulin plus 2 oral agents group (adjusted treatment group difference, −54; 95% CI: −76 to −33) and −54 mg/dL in the patients in the inhaled insulin monotherapy group (adjusted treatment group difference, −69; 95% CI: −91 to −48) compared to 15 mg/dL in the 2 oral agents group. No significant changes were

observed in total cholesterol, LDL cholesterol, or HDL cholesterol.

Weight gain was significantly increased in patients receiving inhaled insulin compared to oral agents alone from baseline to 3 months: 2.7 kg in patients with inhaled insulin plus 2 oral agents (2.7; 95% CI: 1.9 to 3.6) and 2.8 kg in patients with inhaled insulin monotherapy (2.8; 95% CI: 1.9 to 3.6) compared to no weight gain in patients with 2 oral agents only. The number of events of mild to moderate hypoglycemia was 477 in the inhaled insulin plus 2 oral agents group, 365 in the inhaled insulin monotherapy group, and 14 in the 2 oral agents group. This resulted in a risk ratio of 32 (95% CI: 19 to 54) for inhaled insulin plus 2 oral agents and 24 (95% CI: 14 to 42) for inhaled insulin monotherapy compared to the 2 oral agents group. Only 1 case of severe hypoglycemia was reported in the inhaled insulin monotherapy group. The incidence of cough was 14% in the inhaled insulin monotherapy group, 12% in the inhaled insulin plus oral agents group, and 2% in the oral agents group (*P* not reported). No patient discontinued therapy due to cough. No significant changes were observed in FEV₁, FVC, TLC, or DL_{CO}. The percentage of binding insulin antibodies from baseline was 2.89%, 6.14%, and 0% for the inhaled insulin plus 2 oral agents group, inhaled insulin monotherapy group, and 2 oral agents only group, respectively (*P* not reported). The implications of these findings were not associated with allergic adverse effects, hyperglycemic effects, or changes in pulmonary function.

The authors conclude that inhaled insulin improved overall glycemic control when added to or substituted for 2 oral antidiabetic agents. Similar to other insulin therapies, the incidence of hypoglycemia and weight gain was evident. No significant differences were discovered for total cholesterol, LDL cholesterol, HDL cholesterol, or pulmonary function.

Hollander et al³¹ evaluated whether preprandial inhaled insulin given in combination with subcutaneous once-daily long-acting basal insulin could provide comparable glycemic control with a conventional subcutaneous insulin regimen in type 2 diabetic patients previously managed for at least 1 year with at least 2 daily subcutaneous injections of insulin over a 6-month study period (*n* = 293). Patients were randomized to receive either inhaled insulin preprandially plus Ultralente insulin at bedtime or mixed regular/NPH insulin injections given at least twice daily.

In the inhaled insulin group compared to the insulin injections only group, mean A1C levels were reduced from 8.1% at baseline to 7.4%, and 8.2% at

baseline to 7.6%, respectively (95% CI: -0.32 to 0.17). In the inhaled insulin group, 47% achieved a desired A1C <7% compared to 32% in the insulin injections only group (OR: 2.27; 95% CI: 1.24 to 4.14). In the inhaled insulin group, fasting plasma glucose was reduced from 152 mg/dL at baseline to 132 mg/dL at study completion compared with 158 mg/dL to 149 mg/dL in the insulin injections only group (adjusted mean changes from baseline, -15.9 mg/dL; 95% CI: -2.26 to -5.2). The difference between the study groups in adjusted mean changes from baseline in terms of 2-hour postprandial glucose was not significant (-9.41 mg/dL; 95% CI: -26.9 to 8.1). The mean short-acting insulin dose was 24.8 units daily. There were 1104 hypoglycemic events in the inhaled insulin group compared to 1278 events in the insulin injections only group (RR: 0.89; 95% CI: 0.82 to 0.97). In the inhaled insulin group, body weight remained stable at 90.5 kg compared to an increase from 89.2 kg at baseline to 90.6 kg at study completion in the insulin injection only group (adjusted mean treatment group difference was -1.29 kg; 95% CI: -1.98 to -0.59). There were no differences in lipid parameters between the 2 groups.

The authors concluded that for patients who have failed treatment with conventional subcutaneous insulin administered at least twice daily, the benefits of inhaled insulin plus Ultralente were superior. The inhaled insulin group achieved the ADA-recommended A1C goal more often, and fasting plasma glucose was lower with a lower incidence of hypoglycemia and no weight changes compared to the insulin injection only group.

PERSPECTIVES FOR TYPE 2 DIABETES MELLITUS CLINICAL TRIALS

In type 2 diabetes mellitus, the efficacy of inhaled insulin was superior in A1C reduction compared to placebo²¹ or to rosiglitazone.²⁶ Furthermore, for type 2 diabetics failing to achieve adequate control with sulfonylurea and/or metformin, the addition of preprandial inhaled insulin has demonstrated improvement in glycemic control without the need for subcutaneous insulin injections.³⁰ Inhaled insulin also improved overall glycemic control in type 2 diabetics when added to or substituted for 2 oral antidiabetic agents.⁸ Last, when inhaled insulin plus Ultralente insulin was compared with subcutaneous insulin therapy in type 2 diabetes, the reduction in A1C was similar.³¹

The higher incidence of inhaled insulin-induced hypoglycemia was noted when inhaled insulin was compared to placebo,¹ rosiglitazone,²⁶ no inhaled

insulin,³⁰ and a combination of an oral insulin secretagogue with an oral insulin sensitizer.⁸ However, when the rate of hypoglycemia was compared between inhaled insulin plus Ultralente insulin and subcutaneous insulin, the number of events of hypoglycemia was statistically less in the group receiving inhaled insulin.³¹

Inhaled insulin-induced weight gain was evident in trials comparing inhaled insulin to no inhaled insulin,³⁰ as well as a combination of an oral insulin secretagogue plus an oral insulin sensitizer.⁸ However, in 1 trial, body weight remained stable in the inhaled insulin group, whereas there was a significant increase when subcutaneous insulin was used.³¹ Pulmonary side effects were not statistically significant for inhaled insulin compared with baseline FEV₁, FVC, TLC, and DL_{CO} of the lung.^{8,26} A summary of clinical trials for inhaled insulin in type 2 diabetes mellitus can be found in Table II.

ADVERSE EFFECTS OF INHALED INSULIN

The most commonly reported adverse effects with inhaled insulin in clinical trials were weight change, cough, and hypoglycemia.²³ Inhaled insulin has a molecular weight of 5808 daltons, and hence systemic allergic reactions manifesting as an anaphylactoid reaction are rare but have been reported. If a generalized rash with or without pruritus develops, inhaled insulin should be discontinued promptly, and treatment should be started swiftly to prevent the reaction from progressing to dyspnea, angioedema, laryngospasms, and shock. Nonrespiratory adverse reactions reported with inhaled insulin use at an incidence of greater than 1% include dry mouth, chest pain, otitis media, and nonspecific ear disorders.²³ Chest pain was not associated with an increased risk of coronary events and was comparable to subcutaneous insulin.²³

Weight Change

Weight increases were noted in both inhaled insulin and subcutaneous insulin-treated patients in phase III type 1 diabetes trials, with no statistically significant differences found between groups.^{24,25} Weight gain was reported in trials when inhaled insulin was compared to noninsulin products.^{8,21,24,30} However, in trials where inhaled insulin was compared to subcutaneous insulin, weight gain was only demonstrated in patients receiving subcutaneous insulin.³¹ Weight gain is expected as an adverse effect of insulin, especially when insulin resistance occurs. There seems to

be no greater risk of weight gain with inhaled insulin when compared to regular insulin.

Cough

Cough was reported more frequently among patients treated with inhaled insulin.^{24,25} All events were determined to be of mild to moderate severity. The severity of cough reported, incidence, and prevalence declined with continued use of inhaled insulin, although data reported by Skyler et al²⁴ suggests that while new complaints of cough are less likely with a longer duration of inhaled insulin use, existing cough may continue to persist. A mild nonproductive cough generally occurs within seconds to minutes after inhaled insulin is administered and dissipates with continued use, and few patients will need to discontinue therapy due to this adverse effect.

Hypoglycemia

In both type 1 diabetes trials of inhaled insulin, overall hypoglycemia rates (per patient-month) were lower in the inhaled insulin groups (8.6 vs 9 events, respectively; RR: 0.96; 95% CI: 0.93 to 0.99)²⁵ versus the subcutaneous insulin groups (9.3 vs 9.9 events per subject-month, respectively; RR: 0.94; 95% CI: 0.91 to 0.97²⁴). Severe hypoglycemia rates (per 100 patient-months) were higher in the inhaled insulin groups (5.5 vs 4.7 events, respectively; RR: 1.16; 95% CI: 0.76 to 1.76²⁵) compared to the subcutaneous insulin groups (6.5 vs 3.3 events, respectively; RR: 2.00; 95% CI: 1.28 to 3.12²⁴). Among the combined study population who received treatment (n = 662), only 2 patients were reported to withdraw due to hypoglycemia from study treatment, both in an inhaled insulin group.

Mild to moderate hypoglycemia rates were lower in the inhaled insulin groups versus the subcutaneous insulin groups^{24,25,31} and higher in the inhaled insulin groups compared to the noninsulin products.^{8,21,26,30} Among the combined study population of type 1 and 2 diabetes reviewed (n = 1509), only 4 patients experienced severe hypoglycemia. Overall, the incidence of inhaled insulin-induced hypoglycemia was similar to subcutaneous regular insulin in type 1 and type 2 diabetics.

Antibody Formation

Antibodies to insulin, which occur with subcutaneous administration, have also been discovered with the use of inhaled insulin. The effect of these antibodies on postprandial glucose, duration of action of

Table II Summary of Clinical Trials for Inhaled Insulin in Type 2 Diabetes Mellitus

Study design	Randomized, open label, no control	Randomized, open multicenter, parallel, comparative	Randomized, open label, multicenter, parallel, controlled	Randomized, open multicenter, parallel, comparative
Length of study	3 months	3 months	3 months	6 months
Participants	Type 2 diabetes, n = 26	Type 2 diabetes, n = 145	Type 2 diabetes, n = 68	Type 2 diabetes, n = 299
Endpoints evaluated	Safety and efficacy compared to baseline	Safety and efficacy in patients who failed therapy with diet and exercise	Safety and efficacy in patients who failed therapy with 2 oral sulfonylurea and/or metformin	Safety and efficacy in patients who failed therapy with 2 to 3 injections of subcutaneous insulin daily
Treatment	Subcutaneous insulin bid-tid vs inhaled insulin tid plus Ultralente QHS	Rosiglitazone bid vs inhaled insulin tid	Continued therapy with sulfonylurea and/or metformin vs inhaled insulin tid plus continued therapy with sulfonylurea and/or metformin	Inhaled insulin tid plus Ultralente QHS vs mixed regular/NPH insulin bid
Change in A1C	-0.71% in inhaled insulin group (95% CI: -1.00% to -0.41%)	17.9% in rosiglitazone group vs 44% in inhaled insulin group achieved A1C <7% (adjusted OR: 4.43; 95% CI: 1.94 to 10.12)	-2.3% sulfonylurea and/or metformin plus inhaled insulin group vs 0.1% sulfonylurea and/or metformin group ($P < .001$)	-0.7% in inhaled insulin group vs 0.6% in subcutaneous insulin only group (95% CI: -0.32 to 0.17)
Mild/moderate hypoglycemic events	69% episodes with average of 0.83 episodes per month in inhaled insulin group (P not reported)	9 total episodes or 0.05 episodes per subject-month in rosiglitazone group vs 153 total episodes or 0.7 episodes per subject-month in inhaled insulin group (95% CI: 7.51 to 28.83)	57 episodes in sulfonylurea and/or metformin plus inhaled insulin group vs 6 episodes in sulfonylurea and/or metformin group ($P < .001$)	1104 episodes in inhaled insulin group vs 1278 episodes subcutaneous insulin only group (RR: 0.89; 95% CI: 0.82 to 0.97)
Change in weight	-0.3 ± 2.9 kg in inhaled insulin group (P not reported)	+0.8 kg in rosiglitazone group vs +1.9 kg in inhaled insulin group (95% CI: -0.18 to 20.9)	+2.7 kg in sulfonylurea and/or metformin plus inhaled insulin group vs +0.5 kg in sulfonylurea and/or metformin group ($P < .001$)	+0 kg in inhaled insulin group vs +1.4 kg in subcutaneous insulin only group (95% CI: -1.98 to -0.59)

bid, twice daily; tid, 3 times daily; QHS, at bedtime; A1C, glycosylated hemoglobin assay; NPH, neutral protamine hagedorn; CI, confidence interval; RR, risk ratio.

insulin, and clinical safety with a focus on hypoglycemia was recently studied in 47 patients with type 1 diabetes mellitus in a prospective, randomized, open-label, parallel trial.³² Patients received either NPH insulin twice daily together with preprandial subcutaneous regular insulin or NPH insulin twice daily together with preprandial inhaled insulin over a 6-month study period.

For the inhaled insulin and subcutaneous insulin groups, means ($\pm$ SD) for insulin antibodies were 3.5 ± 3.9 and 2.6 ± 4.1 μ U/mL at baseline, respectively, compared with 101.4 ± 140.4 and 4.3 ± 9.4 μ U/mL at the end of the study. Changes from baseline were similar for the inhaled insulin and subcutaneous insulin groups for maximal plasma glucose concentration, area under the plasma glucose concentration-time curve, and duration of action of insulin. Therefore, the authors concluded that insulin antibodies did not impair postprandial glucose tolerance, alter the time action profile of insulin, or affect tolerability. Ostensibly, inhaled insulin does stimulate antibody formation and significantly increases insulin antibody levels, but its sequelae in short-term use seem inconsequential. The long-term significance of insulin antibody formation is unknown and requires further study.

Pulmonary Function

Pulmonary function tests were given during the phase III type 1 diabetes trials at baseline, 12 weeks, and 24 weeks. In both trials, FEV₁, FVC, and TLC demonstrated no differences between treatment groups, but mean DL_{CO} significantly declined in the inhaled insulin group compared with the subcutaneous insulin group. This change was not observed to have any apparent clinical outcomes in the short-term trials. To date, no data specifically addressing changes in pulmonary function tests have been published from the 24-month extension trial enrolling patients from phase III trials, although Fineberg et al³³ reported that there was no correlation between antibody binding and pulmonary function test (FEV₁ and DL_{CO}) changes. Indeed, median percent antibody binding ranged from 28% to 29% with inhaled insulin and 3% to 4% in subcutaneous insulin regimens, after 24 weeks.

No clinically significant differences in pulmonary function with respect to FEV₁, FVC, TLC, or DL_{CO} have been found in patients receiving inhaled insulin.^{8,21,26,30} Nevertheless, because individual patients did experience significant changes in FEV₁ and DL_{CO}, pulmonary function using spirometry should be assessed

at baseline, in 6 months, and annually thereafter. If the FEV₁ declines by greater than 20%, inhaled insulin should be discontinued. In addition, inhaled insulin should be avoided in patients with a baseline FEV₁ or DL_{CO} of 70% or less because the safety and efficacy of inhaled insulin in this population has not been established in trials.

PHARMACOKINETIC DRUG INTERACTIONS

Inhaled Insulin and Albuterol

In an unpublished clinical trial, nondiabetics with both mild ($n = 36$) and moderate asthma ($n = 31$) were administered albuterol 30 minutes prior to inhaled insulin, resulting in a mean increase in AUC and C_{max} of 25% to 50% compared to inhaled insulin alone. Ostensibly, oral bronchodilators and various other inhalation bronchodilators such as levalbuterol, salmeterol, metaproterenol, epinephrine (over-the-counter Primatene Mist), and terbutaline may interact similarly and place the patient at risk of a hypoglycemic episode.²³ The data are unclear as to the appropriate dose adjustment necessary with inhaled insulin when used conjunctively with albuterol, but the manufacturer does not recommend inhaled insulin in patients with underlying lung disease, such as asthma or COPD.

Inhaled Insulin and Chronic Smoking

In smokers, the systemic bioavailability of inhaled insulin increases 2- to 5-fold compared to nonsmokers.²³ Clinical trials ($n = 123$) corroborated that when inhaled insulin was administered to smokers, a faster onset, faster peak effect, and greater total glucose-lowering effect were achieved compared to nonsmokers.²³ Due to the likelihood that smokers will have an unpredictable and exaggerated response to inhaled insulin, inhaled insulin is contraindicated in this population.

Inhaled Insulin and Passive Smoking

In contrast to the effects of chronic smoking on inhaled insulin, exposure to passive smoking for 2 hours in healthy volunteers ($n = 30$) reduced the AUC and C_{max} by 20% and 30%, respectively. Hence, when inconsistent or perplexing effects on prandial glucose control are detected with inhaled insulin, an index of suspicion for the effects of passive smoking should be maintained. The effects of chronic passive smoking on inhaled insulin are unknown but may resemble the

Table III Medications That Interact With Inhaled Insulin²³

Medications that may reduce blood glucose-lowering effect of insulin that may result in hyperglycemia	Corticosteroids Danazol Diazoxide Diuretics Sympathomimetic agents (eg, epinephrine, albuterol, terbutaline) Glucagon Isoniazid Phenothiazine derivatives Somatropin Thyroid hormones Estrogens Progestogens (eg, in oral contraceptives) Protease inhibitors Atypical antipsychotic medications (eg, olanzapine and clozapine)
Medications that may increase blood glucose-lowering effect of insulin that may result in hypoglycemia	Oral antidiabetic products Angiotensin-converting enzyme inhibitors Disopyramide Fibrates Fluoxetine Monoamine oxidase inhibitors Pentoxifylline Propoxyphene Salicylates Sulfonamide antibiotics
Medications that may increase or reduce blood glucose-lowering effect of insulin that may result in hypoglycemia or hyperglycemia	Beta-blockers Clonidine Lithium salts Alcohol Pentamidine

effects of chronic smoking. Indeed, if the mechanism of the interaction between inhaled insulin and smoking is postulated to be due to the effects on inhaled insulin's cytochrome P450 hepatic or lung metabolism and are similar to the effects seen with alcohol, acute smoking could inhibit the metabolism of inhaled insulin, and chronic smoking will induce the metabolism of inhaled insulin. This explains the contradictory effects of onetime passive smoking versus chronic smoking on the metabolism of inhaled insulin. Furthermore, within 1 week of smoking cessation, inhaled insulin systemic levels were reduced by 50%, bringing it to levels similar to nonsmokers, but the $t_{\max}$ and $C_{\max}$ were still similar to that of a smoker.³⁴

The high degree of variability in inhaled insulin absorption on chronic and passive smoking makes it difficult to guarantee an appropriate therapeutic drug level. Hence, inhaled insulin is contraindicated in patients who smoke or have discontinued smoking less than 6 months prior.²³

Inhaled Insulin and Hypoglycemic and Hyperglycemic Agents

A plethora of agents may increase or decrease the effects of inhaled insulin by exerting their inherent glucose-altering pharmacologic effects. Agents that will diminish the effects of inhaled insulin and other insulin therapies can be found in Table III.²³

INHALER TECHNIQUE³⁵

Equipment

Inhaled insulin is available by prescription only and is dispensed as the inhaler device and blister packs containing either 1- or 3-mg doses of inhalation powder insulin. In storage, the base of the inhaler is located within the transparent aerosol chamber. The base contains the medication-dispersing mechanisms. The mouthpiece is located

at the top of the aerosol chamber and may be rotated to open or close.

Administering a Dose

The base of the inhaler is pulled out of the aerosol chamber prior to use and a single unopened blister pack inserted into the base. With the mouthpiece in the closed position, the system is pressurized by pulling down and squeezing shut on the large blue handle on the base. The patient is instructed to stand or sit up straight and to hold the inhaled insulin inhaler upright while facing the blue button. To aerosolize the insulin, the blue button is depressed, and a cloud of insulin should be observed to fill the chamber. If unsuccessful, the blister should be discarded and a new blister inserted. If successful, the patient should promptly breath out normally, rotate the mouthpiece toward himself or herself (into the open position), and place the mouthpiece in his or her mouth. Forming a firm seal around the mouthpiece without obstructing the opening with tongue or teeth, the patient should breathe in slowly and deeply in one breath. The mouthpiece should then be removed and normal breathing resumed. If additional blister packs are required to complete the dose, the gray button should be depressed to allow the used blister to be pulled out. The mouthpiece should be rotated back into the closed position and the process repeated to administer another dose.

Storage and Maintenance of the Inhaled Insulin Inhaler

The base of the inhaler should be pushed back into the aerosol chamber for storage by depressing the 2 chamber release buttons on the base together. The inhaler should be taken apart once a week for cleaning. To clean the aerosol chamber and mouthpiece, warm water and mild soap are recommended; both should be allowed to air-dry completely before reassembling. The base should be held upside down and cleaned with a soft cloth. The release unit should not be cleaned, with care taken not to allow any water to enter. The release unit should be replaced every 2 weeks.

DOSAGE AND ADMINISTRATION

Inhaled insulin is a noninvasive dry-powder insulin inhalation system that is specifically designed to absorb insulin from the lung alveoli. A blister pack of dry powder is inserted into a pulmonary inhaler

Table IV Approximate Guidelines for Initial, Premeal Inhaled Insulin Dose (Based on Patient Body Weight)²³

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

device. The device generates a pulse of compressed air, opens the blister pack, and disperses an aerosol cloud into a holding chamber in which patients may slowly and deeply inhale each dose.³⁶ In contrast to inhaler devices used in asthma and COPD, breath holding at the end of each inspiration has not been shown to affect bioavailability.¹⁸ Each milligram of inhaled insulin is equivalent to approximately 3 units of subcutaneous insulin³⁷ and should be titrated based on blood glucose response.³⁰ Due to rapid-acting pharmacokinetics, inhaled insulin should be administered 3 times daily 10 minutes before meals.³¹ Inhaled insulin is packaged in 1- or 3-mg blister packs together with stabilizers including mannitol, glycine, and sodium citrate. Inhalers, release units, and blisters containing medication should be stored at room temperature. Unit blisters should be used within 3 months after opening the foil overwrap. The inhaler device must be replaced every year, and release units should be changed every 2 weeks. The need to replace these items regularly may contribute to significant cost to patients.

The initial premeal dose for inhaled insulin may be calculated as body weight (kg) $\times$ 0.05 mg/kg rounded to the nearest whole milligram number (eg, 3.7 mg rounded down to 3 mg) (Table IV).

PATIENT SATISFACTION

As one of the primary reasons driving the development of alternative insulin delivery systems, patient satisfaction with insulin therapy has been an additional aspect assessed in several clinical trials. Gerber et al³⁸ compared the results of satisfaction surveys given to 69 patients with type 1 diabetes using inhaled insulin versus subcutaneous insulin regimens, as part of a proof-of-concept study. The inhaled

insulin device used in this study was an earlier prototype of the currently approved inhaled insulin device. Overall satisfaction scores were 35.1% higher for inhaled insulin and 10.6% higher for subcutaneous insulin regimens after 12 weeks ($P < .01$). Likewise, in a comparison reported by Cappelleri et al³⁹ in 47 patients with type 2 diabetes, using the same survey, satisfaction scores were 31% higher for inhaled insulin versus 13% higher for subcutaneous insulin after 12 weeks ($P < .05$). The same survey was again administered to patients enrolled from these 2 trials for a 1-year extension study who were given the choice to continue or switch regimens after the initial 12-week study completed.⁴⁰ Of the eligible patients from the parent studies, 60 were randomized to inhaled insulin and 61 were randomized to subcutaneous insulin. Of those patients who switched therapy, 75.4% ($n = 46$) switched from subcutaneous to inhaled regimens, and 13.3% ($n = 8$) switched from inhaled to subcutaneous regimens. After 1 year, among 102 evaluable patients, overall satisfaction was 37.9% higher for inhaled versus 3.1% higher for subcutaneous insulin regimens ($P < .01$). Among those who switched therapy after the parent studies, those who switched from inhaled to subcutaneous reported lower satisfaction scores at 1 year, whereas those who switched from subcutaneous to inhaled reported greater satisfaction. A different survey instrument used in one of the phase III type 1 diabetes trials²⁵ also reported higher satisfaction scores in inhaled insulin-treated patients ($P < .001$).

FUTURE TREATMENT OF DIABETES MELLITUS

Despite the novel invention of administering insulin via the pulmonary route, diabetes mellitus is quickly becoming known as a "multihormonal" disease state that can no longer be corrected by insulin therapy alone. Some hormones that have been shown to affect blood glucose control include amylin, glucagon, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide, and cholecystokinin octapeptide.⁴¹ Pharmaceutical companies have been targeting these hormones to develop new antidiabetic agents. Three medications that have been recently approved by the FDA include exenatide, an incretin mimetic that stimulates GLP-1 receptors; pramlintide, a synthetic analog of the human neuroendocrine hormone; amylin, which is produced in the pancreas to assist in postprandial glucose control; and sitagliptin, a dipeptidyl peptidase-IV (DPP-IV) inhibitor that improves glucose control by increasing the duration of endogenous GLP-1 activity. Also in clinical

development are LAF237 (by Novartis AG), also a DPP-IV. If well tolerated, these medications may be the future treatment of diabetes mellitus.

CONCLUSIONS

Inhaled insulin appears to offer several advantages that improve compliance and glucose control, including an administration method that does not require a needlestick and ease of administration for patients who have difficulty drawing up insulin or maintaining a regimen of multiple daily needlesticks. Despite the need for storing the inhaler and multiple blister packs, patient satisfaction surveys favor inhaled insulin over subcutaneous insulin. Efficacy data reveal that inhaled insulin is comparable to subcutaneous insulin in terms of time to onset and duration of action but is not more efficacious. Safety concerns are similar to those that should be taken into consideration for any insulin product such as hypoglycemia and weight gain. The long-term pulmonary effects are unknown, and inhaled insulin should be avoided in patients with any existing lung disease or smoking use. Because inhaled insulin is dosed in milligrams instead of units, careful titration and monitoring by clinicians are of utmost importance to avoid adverse effects. Finally, the use of inhaled insulin does not eliminate the need for subcutaneous insulin because basal insulins are not yet available, and thus patients must learn to master 2 different methods of administration.

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