

REVIEW

Pulmonary safety of inhaled insulins: a review of the current data

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ABSTRACT

The availability of non-invasive insulin delivery options for patients with diabetes may encourage earlier insulin use, and thus improve glycemic control and help reduce the diabetes burden. Pulmonary insulin delivery is the most promising alternative with several inhaled insulin systems in development, and the inhaled human insulin Exubera* (insulin human [rDNA origin] Inhalation Powder) has been recently approved in the United States and in the European Union for the treatment of adults with type 1 or type 2 diabetes. Pulmonary function is an important aspect of the safety profile for compounds delivered via the lungs. Pulmonary function with Exubera has been extensively investigated in several completed and ongoing Phase 3 studies conducted in patients with type 1 or type 2 diabetes. A small,

consistent but clinically non-significant decrease in pulmonary function, occurs early, does not progress during 2 years of continuous therapy, and is reversible after discontinuation. A mild, transient cough occurring after inhalation of Exubera is the most common respiratory adverse event observed. Impaired lung function in asthma and chronic obstructive pulmonary disease may modify the absorption of Exubera, whereas active smoking is associated with increased absorption increasing the risk of hypoglycemia. Limited information is available regarding the pulmonary safety of other inhaled insulins, but comprehensive pulmonary studies are anticipated in the future. In preparing this article, the authors searched for references to inhaled insulin in the Medline database and in congress abstracts from 1998 to 2006.

Introduction

Insulin has been the mainstay of diabetes therapy since its discovery in the 1920s, but several barriers to insulin therapy exist¹⁻³. Non-invasive delivery options are under investigation to improve patient acceptability of insulin-based treatment regimens and thereby reduce the long-term burden of diabetes^{4,5}.

Although the oral, nasal, buccal, and transdermal routes have all been investigated, pulmonary delivery is the most promising non-invasive insulin delivery option researched so far⁶. There are currently various inhaled

insulins, including the inhaled human insulin Exubera* (insulin human [rDNA origin] Inhalation Powder), the AERx insulin diabetes management system (iDMS) developed by Novo-Nordisk and Aradigm, AIR inhaler with human insulin inhalation powder (HIIP) developed by Lilly and Alkermes, Technosphere pulmonary insulin developed by MannKind, and the breath-actuated inhaled (BAI) insulin system researched by KOS Pharmaceuticals^{7,8}. Exubera was recently approved in the United States and European Union for use in adult patients with type 1 or type 2 diabetes.

* Pfizer Inc, New York, NY, USA; Nektar Therapeutics, San Carlos, CA, USA

The safety of subcutaneously administered insulin therapy has been well established⁹. An investigation of pulmonary safety is very important in the clinical development programs of compounds delivered via the lungs, such as inhaled insulins. The pulmonary safety profile of Exubera has been extensively researched in several completed and ongoing Phase 3 studies. In contrast, information concerning the pulmonary safety of other inhaled insulin formulations is limited. Based on the literature available to date, this article aims to review the two key questions regarding pulmonary safety – whether there are (1) any environmental or patient-related factors that may affect the absorption of inhaled insulins and (2) any adverse effects of inhaled insulins on pulmonary function.

Factors that influence the absorption of inhaled insulins

For effective absorption of insulin via the lungs, insulin particles must reach the epithelia of the respiratory bronchioles and/or alveoli⁶. To date, two main factors have been identified that affect insulin absorption and bioavailability: smoking and underlying lung disease.

Active and passive smoking

Studies using small molecules such as diethylenetriaminepentaacetic acid (DPTA) have demonstrated that smoking increases lung permeability¹⁰ and thus increases the bioavailability of compounds delivered via the lungs. The clinical development programs of Exubera, AERx (iDMS), and Technosphere inhaled insulin formulations have specifically excluded smokers^{11–14} due to the unknown impact of smoking on insulin bioavailability. However, three studies have specifically investigated the effects of smoking, and smoking cessation, on bioavailability of Exubera and AERx (iDMS) inhaled insulins^{15–17}.

Studies with both Exubera and AERx (iDMS) in non-diabetic subjects consistently reported that smoking greatly increased the rate and extent of absorption of inhaled insulin relative to non-smokers^{15–17} (Figure 1A). Within 1 week of smoking cessation, the bioavailability of Exubera decreased by 50% relative to smokers but was still higher relative to non-smokers¹⁵. Even after 16 weeks of smoking cessation, the effects of smoking on the Exubera pharmacokinetic profile had not returned to levels observed in non-smokers¹⁶. Smoking resumption completely and immediately reversed the effects of smoking cessation¹⁵. The increase in systemic insulin exposure in smokers was associated with an increased risk of hypoglycemia^{15–17}; the risk

of hypoglycemia declined with smoking cessation¹⁶. Because of the rapid changes in insulin bioavailability and the associated risk of hypoglycemia associated with smoking patterns, Exubera is contraindicated in patients who smoke or who have discontinued smoking for less than 6 months prior to starting Exubera therapy. If patients start or resume smoking then they should discontinue Exubera immediately and seek alternative insulin therapy¹⁸. These recommendations are consistent with diabetes treatment guidelines, which state that patients with diabetes should refrain from smoking altogether because of the associated increased risk of cardiovascular events¹⁹. Recommendations regarding smoking and the use of other inhaled insulin formulations are currently not available. The effect of passive cigarette exposure is subject of ongoing studies.

Underlying lung disease

There are various types of underlying lung disease, including asthma, chronic obstructive pulmonary disease (COPD), and respiratory tract infections (RTIs) (e.g. common cold, bronchitis, pneumonia), which may affect the delivery of insulin through the airways, or absorption of insulin in the deep lung, and thereby impact on the bioavailability of inhaled insulins. So far, only data from studies in patients with underlying asthma or RTIs receiving AERx (iDMS) or Exubera are available.

Asthma

Airway caliber can vary greatly between patients, particularly during the course of asthma exacerbations. It is therefore important to investigate whether this and other physiological changes (reduced lung function, pulmonary blood flow, and highly sensitive, hyper-reactive airways²⁰), which occur during asthma, could influence the bioavailability or safety profile of inhaled insulin formulations.

Studies with AERx (iDMS) and Exubera have consistently reported a decrease in inhaled insulin absorption in patients with stable, mild-to-moderate asthma, compared with patients with normal lung function^{18,21} (Figure 1B). With AERx (iDMS), the reduced insulin absorption was coupled with a smaller reduction in blood glucose levels²¹, and could imply that patients with diabetes and asthma may require a higher dose of inhaled insulin to achieve comparable levels of glycemic control. Furthermore, the intrasubject variability of AERx (iDMS) was greater in patients with asthma²¹, which could lead to less predictable dosing effects and a possible increased risk of hypoglycemia or of suboptimal therapy.

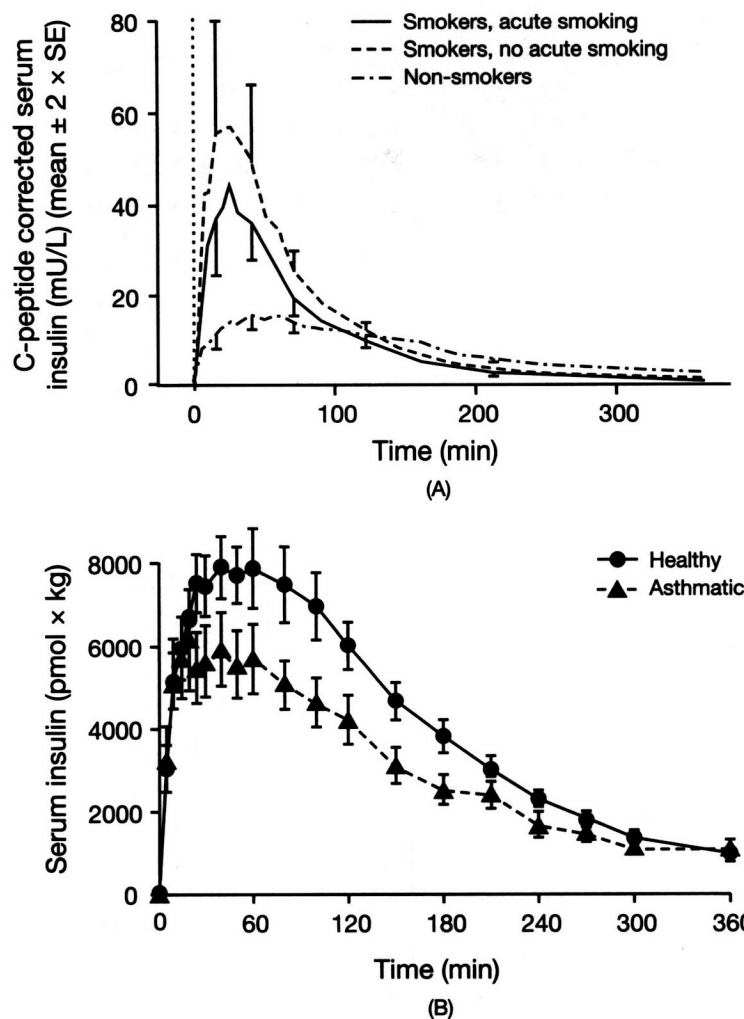


Figure 1. Insulin pharmacokinetics in smokers (AERx, 33.8 IU [A]) and patients with asthma (AERx, 45 IU [B]). Adapted with permission from Himmelman et al.¹⁷ and Henry et al.²¹

Chronic obstructive pulmonary disease

One recent study investigated the pharmacokinetic and glucodynamics of the HIIP insulin administered with the AIR inhaled insulin delivery system in patients with COPD, versus healthy subjects²². Both the mean total insulin exposure (AUC) and metabolic effect were reduced in patients with emphysema and chronic bronchitis, and the intrasubject variability was greater in chronic bronchitis, compared with patients with no COPD. Interestingly, the forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) measured during the glucose clamps declined in both the HIIP and subcutaneous insulin lispro comparator groups, suggesting some effect of study procedures. The decline in relative bioavailability and biopotency, coupled with the relative increase in intrasubject variability observed in this study²², support the need for more extensive studies of the effects of inhaled insulin in patients with COPD. In the meantime, and until further studies to investigate the safety profile of Exubera in patients with underlying lung disease are completed, there are insufficient efficacy

and safety data to support its use in these patients. Exubera is currently contraindicated in patients with poorly controlled, unstable or severe asthma, or severe COPD¹⁸.

Intercurrent respiratory tract infection

Respiratory tract infections are expected to occur with a similar frequency in patients with diabetes, as in the general population. These are associated with complications affecting the upper respiratory tract, which may influence the delivery of inhaled insulin to the deep lung. As with asthma, only information from studies with AERx (iDMS) and Exubera are currently available, although these use different definitions and nomenclature. In AERx studies, 'respiratory tract infection' is defined as acute production of mucus caused by viral infection, whereas the term 'intercurrent respiratory illness' (e.g. bronchitis, upper respiratory tract infection, rhinitis) is used with Exubera studies.

With AERx (iDMS), insulin pharmacokinetics were not significantly different during, and following recovery

from, an uncomplicated acute RTIs²³. Findings from studies with both AERx (iDMS) and Exubera agreed that there were no effects on glycemic control or safety concerns when these inhaled insulins were administered to diabetic patients with this condition^{18,23}. In Exubera studies, 3–4% of patients temporarily discontinued therapy when experiencing these conditions¹⁸. Together, these data suggest that RTIs did not affect the delivery of insulin to the lungs, and patients can continue using the inhaled insulin. However, a *post hoc* analysis of the AERx (iDMS) study found that patients were more resistant to insulin during an RTI, which may present an increased risk of hyperglycemia²³. This is consistent with the current Exubera prescribing information, which recommends close monitoring of blood glucose concentrations during RTIs as individual dose adjustments may be required¹⁸.

In the future, further studies to investigate the full effects of different types of underlying lung disease on the safety profile of the various inhaled insulin formulations are expected.

Impact of inhaled insulins on pulmonary function

One of the most important factors to consider is whether inhaled insulin can affect various aspects of pulmonary safety including lung function, respiratory adverse events, and immunological response within the lungs. Studies with Exubera have extensively investigated all these factors, but so far, information with other forms of inhaled insulin remains limited.

Pulmonary function is an important aspect of the safety profile for compounds delivered via the lungs. This section reviews the key parameters commonly used to measure pulmonary function, factors that can influence pulmonary function measurements, and the available data on the potential influence of inhaled insulins.

Lung function parameters

Several parameters can be used to measure different aspects of lung function, including FEV₁ and diffusing capacity of carbon monoxide (DL_{CO}). FEV₁ measures the volume of air that can be exhaled during the first second of a forced expiratory maneuver. It is used to measure airway obstruction, or changes in airway diameter (e.g. bronchoconstriction or bronchodilation); values are described as a percentage of predicted normal values. An FEV₁ measurement of < 80% of the predicted value with poor reversibility after bronchodilator (< 15%; often < 10% is observed) is

used for confirming the airflow limitation characteristic of COPD^{24,25}, while a large (e.g. > 15%) reversibility in response to bronchodilator therapy suggests the reversible airflow limitation characteristic of asthma²⁰. DL_{CO} reflects oxygen-diffusing capacity; it is influenced by the surface area and thickness of the air-blood barrier, and the speed of blood flow. A reduction in DL_{CO} is indicative of emphysema (loss of surface area) or interstitial lung disease (increased thickness).

Factors that affect lung function

Various factors can affect lung function. These include lung diseases, such as COPD²⁴ or asthma, and patient factors such as history of smoking, age, weight, height, or race^{26,27}. Studies have also shown that non-pulmonary diseases, including diabetes²⁸, can have an impact on overall lung function.

Methodology

One of the challenges of measuring pulmonary function is the large variability between machines and between measurements made on the same machine^{29–31}. Furthermore, some measurements are highly sensitive to patient breathing maneuvers and require a high level of cooperation from the patient. To improve function-testing techniques, and thus ensure good quality data are collected and evaluated, international societies regularly publish practice guidelines^{32–35}. However, in order to obtain reliable information during large-scale multicenter clinical trials, pulmonary function testing needs to be highly standardized between all study centers.

Only studies with Exubera have published pulmonary function data obtained from studies using highly standardized methodology³⁶. At present, there is not sufficient information to determine the level of standardization of pulmonary function testing during the studies using other inhaled insulins (e.g. AERx [iDMS])¹³.

Studies with inhaled insulins

The Exubera clinical trial program has the largest pulmonary safety database of patients with diabetes and includes over 3800 patients, of whom 1977 were treated with Exubera¹⁸. Furthermore, Exubera is the only inhaled insulin formulation that has extensively investigated pulmonary function in comprehensive detail in both patients with type 1 or type 2 diabetes^{11,12,37–41}. Data from other inhaled insulins are limited to two published manuscripts (AERx [iDMS] and AIR [HIIP])^{13,42} and several abstracts (KOS and Technosphere pulmonary insulin)^{43,44}.

All reports published to date with Exubera, AERx (iDMS), Technosphere pulmonary insulin, and AIR (HIIP) agree that the mean treatment group differences in changes from baseline in lung function were small and usually comparable between groups^{11–13,37,39,42,44}. Interestingly, a small decline in lung function over time was seen in patients with diabetes never exposed to Exubera. In most studies with Exubera, patients receiving this insulin experienced greater declines in lung function than patients randomized to comparator therapies. The differences between treatment groups occurred early (within 2 weeks) after treatment initiation³⁸ (Figure 2A) and did not progress thereafter. Investigations with Exubera, AERx (iDMS), and AIR (HIIP) agree that the changes in lung function are not clinically meaningful^{12,13,37,42} and are reversible upon treatment discontinuation^{13,38,40,42}. Data from the Exubera studies suggest that these changes are not driven by statistical outliers, as only a very small percentage of patients experienced a large decline in pulmonary function¹⁸.

Exubera has reported longer-term safety data, demonstrating that the treatment group differences do not progress for up to 2 years of continuous dosing (Figure 2B)⁴⁰. It is also the only inhaled insulin that has reported investigations of the acute effects of administration on lung function immediately after dosing. That study demonstrated no effect of Exubera administration on FEV₁ within 10 or 60 minutes of insulin inhalation⁴⁵.

The Exubera prescribing information in the United States and European Union includes some guidelines on spirometry testing. All patients should have baseline spirometric testing (prior to treatment initiation) and a follow-up measurement after the first 6-months of therapy as indicated¹⁸. Exubera is not recommended for patients with baseline FEV₁ or DL_{CO} < 70% predicted¹⁸. In patients who experience a ≥ 20% decline from baseline in FEV₁, tests should be repeated. If a ≥ 20% decline is confirmed, then Exubera should be discontinued¹⁸. Exubera should also be discontinued in the rare event of bronchospasm¹⁸.

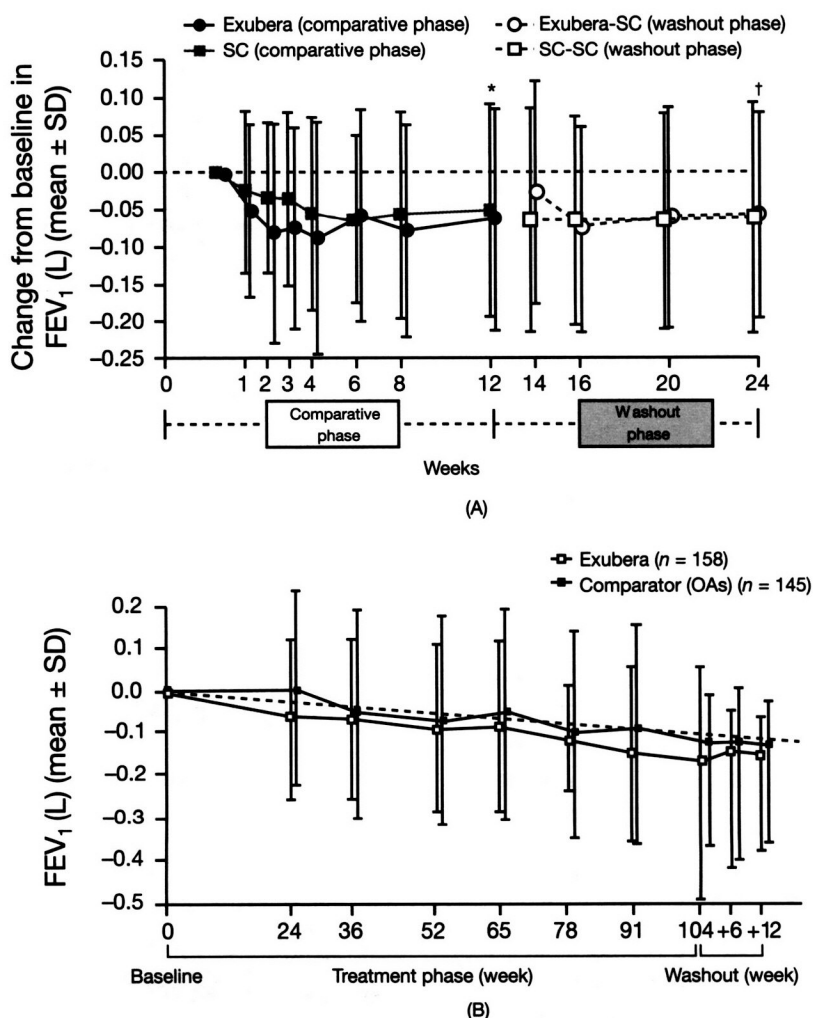


Figure 2. FEV₁ with Exubera inhaled insulin therapy after (A) 12 weeks (standardized testing) and (B) 2 years (non-standardized testing). * -0.009 (95% CI -0.014 to 0.023); † 0.014 (95% CI -0.021 to 0.049). With permission from Brain⁴⁶. FEV₁ = forced expiratory volume in 1 second

Studies with Exubera show that the mean treatment group differences are small, occur early, are non-progressive for up to 2 years and are reversible upon discontinuation. Moreover, treatment group differences were not driven by statistical outliers. Data published so far with other inhaled insulins suggest similar results, although more comprehensive investigations are required.

Respiratory adverse events

As part of the safety profile of any inhaled insulin, it is important to assess whether administration of insulin to the lungs increases the incidence or prevalence of any respiratory adverse events as this may have implications on treatment tolerability. To date, specific respiratory adverse event data have only been published for Exubera and KOS inhaled insulins.

The KOS inhaled insulin formulation reported no difference in pulmonary adverse events⁴³. Several studies with Exubera have reported increased cough. The incidence of cough decreases over time, is predominantly mild to moderate in severity, and rarely results in premature discontinuation of therapies (< 1% across all studies)⁴⁶. A specific cough questionnaire further identified that cough with Exubera is closely associated with dosing, usually occurring within seconds to minutes of inhalation. Furthermore, cough is not associated with declines in lung function or acute bronchoconstriction⁴⁶. Dyspnea, another respiratory adverse event reported with Exubera, is predominantly mild or moderate and only 0.4% of patients discontinued therapy due to dyspnea (vs. 0.1% for patients receiving comparator therapies)¹⁸.

Insulin antibodies

Delivery of proteins such as insulin to the pulmonary mucosa could induce an immune or allergic reaction⁴⁷, which may have implications on safety or effectiveness of treatments. Of the inhaled insulins in development, the insulin antibody response with Exubera has been investigated in the most comprehensive detail⁴⁸. Insulin antibody data have also been researched in one study with AERx (iDMS) and another study using the Technosphere formulations^{13,44}. Interestingly, no antibodies were observed in one study with the Technosphere system¹³, while no data are available to date on insulin antibody levels when using the AIR (HIIP) or KOS inhaled insulin formulations.

A large meta-analysis of several Exubera Phase 2/3 studies⁴⁸ and one study with AERx (iDMS)¹³ showed higher insulin antibody levels with inhaled insulins versus comparator therapies. With Exubera, this increase in insulin antibodies was not significantly correlated with parameters of insulin pharmacodynamics⁴⁹, glucose control or safety profile⁴⁸. The time course of insulin antibody formation was also temporarily dissociated from the time course of changes in FEV₁. There was a lack of correlation in insulin antibody levels and lung function and, more importantly, a dissociation following cessation of therapy, when the diminution of insulin antibody levels lagged behind the resolution of mean FEV₁ changes. These results suggest that there is no causal relationship between insulin antibody formation and lung function changes in diabetic patients treated with inhaled insulin, and suggests that these two effects are mediated by different mechanisms⁴⁵. Other inhaled insulin formulations currently in development have only very limited data available, so more detailed studies are expected in the future.

Conclusion

Smoking and underlying asthma alter inhaled insulin bioavailability. As a result, Exubera is contraindicated in patients who smoke, and its use is not recommended in patients with poorly controlled or unstable lung disease. Exubera has the most extensively researched pulmonary safety profile, which demonstrates that inhaled Exubera is generally well tolerated. The mean treatment group changes in pulmonary function were small, not clinically relevant, non-progressive for up to 2 years of continuous dosing and reversible upon discontinuation of treatment. The limited data available with other inhaled insulins currently in development are in general agreement with Exubera studies, although more comprehensive safety studies are expected in the future.

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Note on research

In preparing this article, the authors searched for references to inhaled insulin in the Medline database

and in congress abstracts of the American Association of Clinical Endocrinologists (AACE), the American Diabetes Association (ADA), the American Thoracic Society (ATS), the European Association for the Study of Diabetes (EASD) and the European Respiratory Society (ERS) from 1998 to 2006.

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