



ELSEVIER

LETTERS

The Clinical Relevance of Inhaled Insulin in the Diabetic Lung

To the Editor:

We read with interest the recent review by Hsia and Raskin¹ on pulmonary dysfunction in diabetes and its relevance for the potential use of inhaled insulin. The authors focus on 3 unresolved issues associated with inhaled insulin that could affect the progression of diabetic pulmonary dysfunction. Their first concern is the higher level of insulin-binding antibodies associated with inhaled delivery, which could act as a reservoir for prolonged insulin release. Secondly, it is noted that repeated alveolar deposition of insulin may induce unintended local effects on microvascular reserves, although little or no change in lung diffusing capacity (DL_{CO}) has been observed in controlled clinical trials to date.²⁻⁴ Finally, the authors suggest that a potential reciprocal interaction may exist between inhaled insulin and coexisting lung disease, citing the effects of smoking and asthma on insulin absorption as evidence.

Although we welcome this cautious approach to inhaled insulin, we feel that there is sufficient evidence to address these concerns. A number of recent and ongoing trials have investigated the effect of Exubera (one of the inhaled insulins currently under development by Pfizer and Sanofi-Aventis) with respect to insulin antibodies, pulmonary function, and smoking. In a 2-year study investigating the antibody response in patients with type 1 or type 2 diabetes treated with either inhaled or injected insulin, no adverse clinical consequences were observed despite the presence of more insulin-binding antibodies in the Exubera group. In addition, there were no correlations between increased antibody binding and glycemic control or insulin dose requirements.⁵ In terms of the effect of Exubera on pulmonary microvascular reserve, the results of a long-term controlled safety study in type 2 diabetes demonstrated no discernable effects on pulmonary gas exchange after 2 years of continuous treatment.⁶ Ongoing studies using robust methodology are investigating the effect of inhaled insulin therapy on pulmonary gas exchange.⁷

The increased pulmonary absorption of inhaled macromolecules such as DTPA in active smokers is well recognized.⁸ Similarly, the absorption of Exubera has been demonstrated to be significantly increased in active smokers.⁹⁻¹¹ As a consequence, active smokers have been excluded from

all clinical studies of Exubera. Subjects with mild-to-moderate asthma and chronic obstructive pulmonary disease (COPD) have been allowed to participate in phase 3 clinical studies of Exubera and to date have experienced safety and efficacy outcomes similar to subjects without these disorders. Prospective studies evaluating the safety and efficacy of inhaled insulin in diabetics with underlying asthma and COPD are ongoing.

Although we recognize that some of the safety issues raised in this letter are still unresolved, the available data from an extensive series of clinical trials strongly suggest that insulin can be safely and effectively administered via inhalation. Ongoing trials should confirm if there are clinically important interactions between inhaled insulin therapy and the lung function of diabetics. Rather than contribute to existing complications, the introduction of a method of delivering insulin that patients overwhelmingly prefer to subcutaneous injections¹² offers the potential to improve long-term glycemic control and ameliorate diabetic complications such as diabetic microangiopathy.

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The Reply:

We appreciate the comments of Teeter and Becker, and agree with them that current trials on the use of inhaled insulin in treating type 1 and type 2 diabetes show encouraging results that support its efficacy and effectiveness, either as a supplemental regimen or as an alternative route for reducing the dose or frequency of subcutaneous insulin injections. We already have noted that patient satisfaction with inhaled insulin is consistently high and the side effects minor.¹ It is also encouraging to see that the up to 10-fold sustained elevation of median anti-insulin antibody level associated with inhaled insulin use causes no apparent ill effect during 2 years of follow-up.² The higher antibody level is at least partly related to the low biological availability of inhaled insulin, necessitating an inhalation dose more than 10-fold that with subcutaneous injection, in milligram quantities.³⁻⁵ Asthmatic subjects absorb less inhaled insulin and require an even larger amount to achieve the desired result.⁶ Smoking definitely alters inhaled insulin delivery as noted by Teeter and Beck, but until smokers are included in large extended clinical trials, the effect of smoking on inhaled insulin use cannot be determined.

Insulin is a potent mitogen and growth factor for various cell types, including alveolar epithelial cells^{7,8} and airway smooth muscle cells,⁹ and it augments DNA synthesis induced by other growth factors.⁹ Insulin interacts with epithelium-derived nitric oxide to modulate airway smooth muscle contraction in vitro.^{9,10} Insulin also causes pulmonary arterial vasodilation and ameliorates hypoxia-induced pulmonary vasoconstriction in isolated pulmonary arteries.¹¹ In vivo animal studies show that insulin increases phosphatidyl choline and disaturated phosphatidyl choline contents in fetal lung, an effect additive with hydrocortisone.¹² In addition, insulin administration readily reverses changes of alveolar structure¹³ and connective tissue metabolism¹⁴ caused by experimental diabetes. Direct human data addressing these aspects of insulin action are nonexistent, but clearly the known biologic activities of insulin on respiratory tissue affect the diabetic human lung receiving repetitive supra-physiologic doses of insulin over prolonged

periods from years to decades. In addition, interactions between chronic inhaled insulin use and lung maturation, aging, and concurrent primary parenchymal lung disease all remain to be defined. Relative to the chronicity of the diabetic condition, 2 years is a relatively short follow-up period; more extended trials will be needed to resolve long-term safety issues and to determine whether or how inhaled insulin alters the development or progression of diabetes-related pulmonary dysfunction. For these reasons it is prudent to cautiously approach the application of this novel exciting technology and refrain from drawing conclusions until long-term safety data are actually at hand.

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