Inhaled Insulin in Clinical Practice—A Focus on Pulmonary Safety

a report by
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DOI: 10.17925/USE.2007.00.1.44

Inhaled Insulin—A New Therapeutic Option

Inhaled insulin represents the first non-injectable option available for insulin therapy since the discovery of insulin in the 1920s. The first inhaled insulin to gain regulatory approval is Exubera (insulin human [rDNA origin] inhalation powder, Pfizer). In January 2006, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) approved Exubera for the treatment of adult patients with diabetes mellitus. Several other inhaled insulins are in development, including a liquid formulation (AERx iDMS, Novo Nordisk/Aridigm) and other human powdered formulations (AIR insulin system, Eli Lilly/Alkermes; Technosphere insulin, MannKind).

As inhaled insulin is a novel drug substance intended for chronic administration via a novel route, respiratory safety has been a cause of concern. Consequently, the respiratory safety of inhaled insulin has been studied extensively in both type 1 and type 2 diabetes populations. This brief review will examine the available safety data for inhaled insulin in terms of pulmonary function.

The Inhaled Route of Administration

The pulmonary route has been the most widely researched non-invasive alternative to subcutaneous administration of polypeptides. It offers the greatest potential for systemic insulin delivery, since some of the features that make the lung so well suited for gas exchange—particularly its huge surface area—also make it an ideal organ for absorption of small molecules into the bloodstream. Human lungs have a large (greater than 100m^2), thin (0.1–0.2 micrometers), highly vascular epithelial surface area, permitting rapid passage of insulin from the alveoli into the systemic circulation.[1] The lungs tolerate the administration of polypeptides immunologically and the distal airways lack significant muccocilliary transport, allowing time for absorption. The main disadvantage of inhaled drug delivery is the requirement for a specific particle size (1–3 micrometers) to achieve deep alveolar deposition.[2] Small peptides—such as insulin (approximately 6,000 daltons)—are readily absorbed, provided they are administered in the form of particles with the ideal particle size.

Factors Affecting Inhaled Insulin Absorption

Exposure to Tobacco Smoke

The use of inhaled insulin is contraindicated in patients who smoke. For safety purposes, patients must have stopped smoking more than six months earlier in order to be considered for treatment with Exubera. This is because the bioavailability of insulin is increased in chronic smokers compared with non-smokers, even some months after smoking cessation. Studies examining inhaled insulin absorption have shown that active smoking increases absorption of inhaled insulin two- to five-fold, which can expose the patient to the risk of hypoglycemia. However, the mechanism by which smoking affects inhaled insulin absorption is still unknown. This is a public health issue and young type 1 diabetics in particular should be told not to commence smoking if they want to benefit from therapy with Exubera. In contrast, the absorption of subcutaneous insulin is not affected by smoking.[3,4]

The effect of passive smoking on the absorption of inhaled insulin has also been studied and—in contrast to the effects of active smoking—the investigators reported that that acute passive smoking caused a decrease in lung permeability, which in turn resulted in a decrease in inhaled insulin bioavailability. However, this did not create a risk for hypoglycemia.[5] Likewise, smoking a single cigarette is associated with a decrease in insulin absorption.

Lung Disease

The use of inhaled insulin is altered in patients with unstable or poorly controlled lung disease. Therefore, inhaled insulin is not recommended for use in patients with asthma, chronic obstructive pulmonary disease (COPD), or interstitial lung disease; patients with screening forced expiratory volume in 1 second (FEV1) <70% predicted; and patients with screening diffusing capacity of carbon monoxide (DLCO) (if performed) <70% predicted. Moreover, in the majority of the clinical studies involving inhaled insulin, patients with the characteristics detailed above were excluded.

In a recent study, the effects of prior administration of the bronchodilators albuterol and fluticasone were assessed on inhaled insulin pharmacokinetics. In the absence of a bronchodilator, mild to moderate asthma was associated with reduced pulmonary absorption of inhaled insulin. Inhaled insulin absorption increased following the administration of albuterol 30 minutes before inhaled insulin relative to inhaled insulin administration without bronchodilator treatment. Prior albuterol administration increased mean maximum insulin concentration (C_{max}) amd area under the curve (AUC0–360) by 25–35% in patients with mild asthma and by 45–50% in patients with moderate asthma.[6] Accordingly, patients should be informed of the possibility of hypoglycemia should they use Exubera in combination with an inhaled bronchodilator.

The potential clinical implications of intercurrent upper respiratory tract infections on inhaled insulin therapy have also been studied. A retrospective analysis of pooled data from 14 controlled phase II and III clinical trials showed that inhaled insulin was well tolerated and

efficacious in the presence of intercurrent upper respiratory tract infections in both type 1 and type 2 diabetes patients.[7] Although current data in patients with pneumonia are insufficient to make a clear statement, it may be prudent to err on the side of safety and to switch patients to conventional insulin until the pneumonia resolves.

Effect on Pulmonary Function

Concerns regarding the potential for pulmonary toxicity with chronic use of inhaled insulin have been raised due to the growth-promoting and immunogenic properties of insulin. Moreover, small reductions in lung function have been reported in both type 1 and type 2 diabetes patients. Therefore, any further effect by inhaled insulin on this reduced baseline pulmonary function may have a potentially clinical impact.[8–10] Consequently, the safety profile of inhaled insulin on pulmonary function has been extensively studied throughout its clinical development.

Cough

In clinical trials, cough of mild to moderate severity was the most common pulmonary symptom associated with inhaled insulin. In a meta-analysis, cough was reported more frequently in patients receiving inhaled insulin compared with patients treated with subcutaneous insulin and/or an oral antihyperglycemic agent (16.9 versus 5%, respectively; risk ratio 3.52). Cough generally occurred within seconds or minutes of inhaled insulin administration and was mild to moderate in severity. Cough was seen to diminish with time on therapy.[11] Only 1–1.6% of trial subjects discontinued with inhaled insulin therapy due to cough.[12] It has been reported that cough is not associated with an increased level of insulin antibodies.[11]

Forced Expiratory Volume in 1 Second

In short-term studies of 12–24 weeks, exposure to inhaled insulin has been associated with small but consistent reductions in FEV1 compared with comparator groups treated with subcutaneous insulin and/or oral agents.[13–18] The magnitude of reduction in FEV1 was similar in both type 1 and type 2 diabetes patients.

In a 12-week study on type 1 diabetes patients, inhaled insulin produced a 65ml decline in baseline FEV1 compared with 53ml in subcutaneous insulin-treated patients. The decline in FEV1 occurred early and was not progressive (the slope of the FEV1 versus time curve was similar in the inhaled insulin-trated group and the control group). Moreover, differences in FEV1 between the treatment groups resolved within two weeks of discontinuation of inhaled insulin.[15] Similarly, in a 24-week cross-over study, small reductions in baseline FEV1 were observed within two weeks of initiating inhaled insulin therapy and were reversible upon discontinuation of therapy.[18]

The results of a longer-duration study of inhaled insulin in type 1 diabetes patients indicate that the initial reductions in FEV1 occurred within the first three months of therapy and were significantly different between treatment groups following one year of therapy (mean annual rates of decline in FEV1 following one year of therapy were -0.051l/year with inhaled insulin and -0.034l/year with subcutaneous insulin). However, this decline was not progressive. After two years of therapy, the mean annual rates of change in FEV1 were -0.041l/year and -0.031l/year in the inhaled insulin and subcutaneous insulin groups, respectively (non-significant mean difference).[19] The interim analysis of a long-term study assessing pulmonary safety following discontinuation and re-administration of inhaled insulin human therapy in adults with type 1 diabetes indicates that small, non-progressive treatment group differences in change from baseline FEV1 occurred early during the comparative phase and were resolved upon discontinuation of inhaled insulin. The patients in the study received either inhaled insulin or subcutaneous insulin for up to two years in an ongoing, open-label study (comparative phase), followed by six months of subcutaneous insulin (follow-up phase) and a six-month extension phase during which all patients received their original randomized therapy.[20]

The FDA's statistical review of the safety of the inhaled insulin included a pooled analysis of data from phase II and III studies for type 1 diabetes. The pooled data included data from six separate studies involving 686 adult subjects in the inhaled insulin groups and 692 subjects in the comparator subcutaneous insulin group. At years one and two, there was a significant difference in FEV1 between the inhaled insulin and comparator groups, in favor of the comparator.[21]

The effect of inhaled insulin on FEV1 has also been extensively studied in the type 2 diabetes population. In a 12-week study assessing the safety and efficacy of inhaled insulin in type 2 diabetes, there was no significant difference in small reductions in FEV1 between the inhaled insulin group and the oral-agent group.[13] In a 24-week study, inhaled insulin was compared with subcutaneous insulin in patients with type 2 diabetes. Mean changes in FEV1 were small and comparable between the two treatment groups.[14] It must be noted that within these clinical trials, dyspnea has been observed in approximately 4% of patients on the inhaled insulin Exubera compared with 3% on comparator drugs. There were a few outliers in the studies who did not show a significant drop in FEV1; in most of these cases there was the compounding influence of other factors, particularly congestive heart failure.

In two studies of longer duration, the pulmonary safety of inhaled insulin as adjunctive therapy with oral agents was assessed in type 2 diabetes patients. A pooled analysis of the data revealed that changes from baseline FEV1 were slightly larger for the inhaled insulin group compared with the oral-agent group at 24 weeks, but this difference did not increase further at 52 weeks.[22] Indeed, the adjusted difference between groups decreased at 36 weeks and there was no discernable treatment group difference in FEV1 12 weeks after discontinuing two years of therapy.[23] An interim analysis of data presented at the American Diabetes Association (ADA) 67th Scientific Sessions indicates that inhaled insulin produces a small non-progressive difference in FEV1 compared with subcutaneous insulin over two years. The type 2 diabetes patients received inhaled insulin for up to two years in an ongoing, open-label study (comparative phase), followed by six months of subcutaneous insulin (follow-up phase) and a six-month extension phase during which all patients returned to their original randomized therapy. Treatment group differences occurred early during the comparative phase, were completely resolved upon discontinuation of inhaled insulin, and recurred to the same magnitude during the extension phase.[24]

An FDA pooled analysis, which included results from eight studies involving 1,277 (inhaled insulin groups) and 1,132 (comparator groups receiving either subcutaneous insulin and/or oral antihyperglycemic agents) type 2 diabetes patients, showed that the absolute difference between inhaled insulin and comparator groups at one year was statistically different in favor

of the comparator groups). At two years, the differences were comparable between groups.[21] Thus, inhaled insulin therapy produces small, significant decrements in FEV1, with absolute differences of 44 and 41ml at one and two years, respectively, compared with comparator groups. These changes occurred early, were non-progressive, and resolved following discontinuation of inhaled insulin.

Diffusing Capacity of Carbon Monoxide

Short-term studies of 12–24 weeks have shown that inhaled insulin produces a small but consistent decrement in DLCO compared with those on oral antidiabetes medications or subcutaneous insulin.[13–18]

In a 24-week study with type 1 diabetes patients, treatment with inhaled insulin resulted in a DLCO decrease of 0.75ml/min/mmHg compared with a decrease of 0.23ml/min/mmHg in the subcutaneous insulin group. The difference between groups was statistically significant.[16] In a 12-week trial in patients with type 1 diabetes, inhaled insulin treatment resulted in a decrease in DLCO of 1.2ml/min/mmHg compared with baseline. Subcutaneous insulin resulted in a 0.5ml/min/mmHg decrease from baseline.[13] A 12-week study in patients with type 2 diabetes randomized to either inhaled or subcutaneous insulin revealed that inhaled insulin was associated with a greater mean DLCO decrease from baseline than in the subcutaneous insulin group.[14] The mean difference in DLCO between groups in the latter two studies were not statistically significant.

Longer term studies have been conducted in both type 1 and type 2 patients. In two longer term studies, a pooled analysis of the data showed that inhaled insulin as adjunctive therapy with oral agents in type 2 diabetes patients for up to two years produced no significant differences for DLCO between groups after one year and no discernable treatment group differences in DLCO 12 weeks after discontinuing two years of therapy.[22,23] Cefalu and colleagues showed that inhaled insulin treatment in adults with type 2 diabetes was associated with small, non-progressive treatment group differences in DLCO that were reversible upon discontinuation of inhaled insulin.[24] Hollander and colleagues showed similar results in type 1 diabetes patients.[20]

An FDA pooled analysis indicates that changes in DLCO for inhaled insulin and comparator groups for both type 1 and 2 diabetes populations are small and occur in the first 12 weeks. Interestingly, between-group differences (inhaled insulin versus comparator) in DLCO in the type 1 diabetes population are statistically significant. In contrast, in patients with type 2 diabetes the-between group differences were not significantly different from changes observed in the comparator groups.[21]

Conclusion

Inhaled insulin is a recent therapeutic advance for the treatment of diabetes. It offers a convenient, as well as accepted, alternative to injected insulin. However, due to its route of delivery, the main concern with the use of inhaled insulin is its effect on pulmonary function. Both short- and long-term studies have shown small but consistent treatment group differences in lung function tests (FEV1 and DLCO) with inhaled insulin. However, these changes—as well as being small—occurred early after treatment initiation, were non-progressive for up to two years, and were reversible following discontinuation of inhaled insulin therapy. Longer term safety studies beyond two years are needed to ensure that the small difference in lung function does not progress with time during long-term exposure to Exubera; while such studies are ongoing, evidence to date suggests that inhaled insulin offers a viable therapeutic option for the treatment of diabetes. ■

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