EDITORIAL

Inhaled Insulin and Its Effects on the Lungs

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Diabetes mellitus is a highly prevalent, chronic, progressive, metabolic disease with high morbidity and mortality that has taken on truly epidemic proportions.[1] Management of acute metabolic abnormalities and prevention of chronic vascular disease require early diagnosis, ongoing medical attention, and complex multifactorial treatment, whose difficult goal is to maintain glycosylated hemoglobin (hemoglobin A_{1c}) levels at 7% or less. This goal is even more difficult in patients with type 1 and type 2 diabetes who require insulin therapy; they may be anxious about the painful injections, are at greater risk of hypoglycemia, and can erroneously believe that insulin use indicates a marked worsening of the disease and certain social limitations. Almost from the moment insulin was discovered, such drawbacks motivated efforts to develop insulin that did not need to be injected. Most of the efforts failed—with the exception of inhalation systems, which have enabled the development of (preprandial) inhaled liquid and dry-powder formulations of rapid-acting recombinant human insulin analogs, such as Exubera, AERx insulin Diabetes Management System (iDMS), and AIR human insulin inhalation powder (HIIP). Exubera has recently been approved in the United States of America and the European Union as an alternative to preprandial subcutaneous insulin.

Pulmonary delivery has been shown to be efficacious: the lungs absorb aerosolized insulin just as they do other molecules. Absorption is facilitated by the extensive gas exchange surface of the lungs (40 m^2 to 140 m^2) composed of more than 500 million alveoli with a thin epithelial barrier (0.1 μm to 0.3 μm); the surface is characterized by extensive vascularization, few proteases, mucociliary clearance, and excellent bioavailability. Pulmonary delivery also avoids the first pass through the liver, thus enabling rapid absorption and ensuring efficacy when administered as preprandial insulin.[2] Since inhaled insulin is mainly retained in the oropharynx and in the upper and middle respiratory apparatus, its bioavailability is approximately 10% that of subcutaneous insulin. The pharmacokinetics of inhaled insulin depends on certain variables: the diameter of the inhaled particles, from 1 μm to 5 μm (aerodynamic size), necessary for the insulin to reach the alveoli and pass through to the circulatory system; the breathing pattern of the patient, since the reproducible response to inhaled insulin requires controlled breathing; and drug clearance in the alveoli, most commonly via macrophage phagocytosis (transcytosis), and some paracellular diffusion.[3,4]

Experimental studies on inhaled insulin have identified no general or local (pulmonary) toxic effects, no changes in respiratory parameters, no antibodies, and no carcinogenesis—inhaled delivery is therefore considered to be safe. Most phase II and III clinical studies on inhaled insulin were carried out using an open-label design (not double-blind) in a total of more than 3200 adult nonsmoking patients with type 1 and type 2 diabetes and no lung disease or microvascular conditions; these studies found that the pharmacokinetics and pharmacodynamics of inhaled insulin are faster-acting than regular insulin and have a time-action profile similar to that of ultra-fast-acting subcutaneous insulin analogs (lispro and aspro).[5-9] Maximum plasma concentration (C_{max}) of inhaled insulin (mU/L) peaked higher and sooner than with subcutaneous insulin—as did the area under curve (mU/L per hour) ($AUC_{0\text{-}2\,h}$). $AUC_{0\text{-}6\,h}$ and individual variation were similar in both groups. Thus the profile of inhaled insulin mimics physiological insulin response to food more closely than does subcutaneous insulin.

The efficacy of inhaled insulin in patients with type 1 and type 2 diabetes, as measured by changes from baseline in hemoglobin A_{1c}, by the percentage of patients who reached the goal of 7% hemoglobin A_{1c} or less, by pre- and postprandial blood glucose levels, and by hypoglycemic event rates and severity, was similar to that of subcutaneous insulin. Immunoglobulin G anti-insulin antibodies were observed to increase markedly[10] (with greater intensity in diabetes type 1 than in type 2) then stabilize after 6 to 12 weeks, with no repercussions in respiratory or metabolic parameters (hemoglobin A_{1c}, pre- and post-prandial blood glucose). These increases returned to normal on discontinuing treatment.

To compare the effects of inhaled insulin with those of subcutaneous insulin on lung function, more than 43 000 assessments were performed on approximately 4000 adults with type 1 and type 2 diabetes but no lung disease or vascular conditions, in order to analyze changes in lung function and corresponding reversibility in the short term (at 6 months of treatment) and long term (at 2 to 4 years of treatment). The primary endpoints were forced expiratory volume in 1 second (FEV_1) to measure lung function, and pulmonary carbon monoxide diffusing capacity to measure gas exchange in the alveoli. From the first week, slight, nonprogressive decreases in FEV_1 (<1%–5%) were

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observed with inhaled compared with subcutaneous insulin; the decreases stabilized at 3 to 6 months and reversed within few days after withdrawing the drug.[10-12] There was no evidence of acute postinhalation effects on respiratory parameters at 10 minutes and at 60 minutes. Before treatment with inhaled insulin, therefore, baseline spirometry is recommended in order to rule out previous lung disease and to obtain data for subsequent comparison. Spirometry should be repeated at 6 months. If, at the end of the 6-month period, FEV_1 has decreased by less than 15%, annual control should be performed; if FEV_1 decreases 15% to 20%, tests should be performed at 3 months; if FEV_1 decreases 20% or more in 2 tests, treatment should be interrupted.

The most frequent side effect was light to moderate cough, which appeared shortly after inhalation and decreased over time. Only 1% of patients discontinued the treatment regimen due to this cough. The cough was not associated with changes in lung function. No adverse events were observed except slight dry mouth and throat, and events characteristic of insulin use.[10]

The rate of comorbidity of diabetes and lung disease is very high; 14.1% of diabetic patients are hospitalized for lung disease,[13] which is the second most common cause of death after cardiovascular processes among diabetic patients. Surprisingly few studies on inhaled insulin have been carried out in this population group in view of the fact that many are smokers. Although, as explained below, outcomes with inhaled insulin are cause for optimism, they should be carefully evaluated. Studies of larger populations are needed to analyze the real efficacy of inhaled insulin. The few trials reported in the literature were carried out with Exubera insulin, AERx (iDMS) insulin, and AIR (HIIP) insulin. Similarly, the medical literature does not include studies on the comorbidity of diabetes and commonly associated small vessel disease (diabetic capillaropathy), which, given that it is so widespread, could affect the capillaries of the alveolocapillary membrane with negative repercussions on diffusion, in turn affecting the pharmacokinetics and pharmacodynamics of inhaled insulin.

The following questions are therefore hard to answer: What impact do inhaled insulin analogs have on the lung function of patients with diabetes and pulmonary or vascular comorbidity? Are inhaled insulin analogs indicated for this type of patient? Are inhaled insulin analogs efficacious in this type of patient?

1. Inhaled insulin and smoking. Acute effects of smoking include irritation of the mucosa, changes in muscle tone, increasing vasoconstriction, and harmful effects on regional blood flow distribution.[14] In smokers the pharmacokinetics and pharmacodynamics of inhaled insulin are affected, thereby increasing the bioavailability of the insulin and, in turn, accentuating hypoglycemia. These processes are reversed on smoking cessation. Randomized crossover trials carried out in healthy subjects and in diabetic smokers and nonsmokers showed that the time to maximum plasma concentration was shorter in smokers, regardless of whether they had just been smoking, than in nonsmokers.[15-18] It was found that insulin C_{max} was threefold higher in smokers possibly because of low pulmonary surfactant levels; it was also found that insulin C_{max} decreased 23% as a result of smoking immediately before inhaling the drug—probably due to the purely physical phenomenon of the presence of smoke particles in the alveoli.

2. Inhaled insulin and asthma. One of the most important studies on the pharmacokinetics and pharmacodynamics of inhaled insulin in patients with asthma is by Henry et al.[19] These authors compared nonasthmatic subjects and nondiabetic patients with stable, mild, or moderate asthma. The time to C_{max} after intake of 1.57 mg of AERx (iDMS) inhaled insulin was 55 minutes in both groups, although the asthmatic patients absorbed less insulin owing perhaps to airway restriction.[17] Inhaled insulin produced a greater $AUC_{0\text{-}360\ min}$ in healthy subjects than in asthmatic patients (P=.013), with no difference in C_{max} between the 2 groups. A greater reduction in blood glucose levels was observed in the healthy subjects, measured by $AUC_{0\text{-}360\ min}$ (P=.007). Intraindividual variation was greater in the asthma group. The asthmatic patients may need a larger dose of inhaled insulin to achieve levels of glycemic control similar to those of patients with normal respiratory function.[18]

Although the effect of bronchodilator drugs on inhaled insulin in patients with asthma is of interest, there are few studies on the subject. In an open-label crossover randomized study of 67 nondiabetic volunteers with mild to moderate asthma, Fountaine et al[20] compared the effects on the pharmacokinetics of inhaled insulin of 180 µg of albuterol (a short-acting β-agonist) or 440 µg of fluticasone (an inhaled corticosteroid) inhaled immediately before or after inhaling the insulin. Only albuterol improved the pharmacokinetic profile of the inhaled insulin, increasing C_{max} and the $AUC_{0\text{-}360\ min}$ from 25% to 30% in the patients with mild asthma and from 45% to 50% in those with moderate asthma.

In asthma patients, no significant changes were observed in FEV_1, forced vital capacity (FVC), and FEV_1/FVC at 30, 60, and 360 minutes after inhalation compared to baseline values (30 minutes before dose)—not even with larger doses (135 IU); nor were episodes of bronchial hyperreactivity observed.

3. Inhaled insulin and chronic obstructive pulmonary disease (COPD). The only reported study on inhaled insulin and COPD is that by Rave et al,[21] who compared the pharmacokinetics and pharmacodynamics of AIR inhaled insulin (iDMS) with subcutaneous lispro in 15 healthy nonsmokers and 30 nonsmokers with moderate COPD (IIA or IIB), 15 with chronic bronchitis and 15 with emphysema. The authors reported reduced absorption and metabolic effects in COPD patients. These effects were more marked in those with chronic bronchitis compared to those with emphysema. Although FEV_1 and FVC decreased in both COPD groups, the decrease was not significant. The only relationship reported by the authors was between pulmonary carbon monoxide diffusing capacity and pharmacokinetic response, including the AUC from dose administration to the last sampling time ($AUC_{0\text{-}t}$) and C_{max}, an observation which may partly explain the reduced viability of inhaled insulin in patients with COPD.

They suggested that the relationship arises because of pulmonary structural abnormalities, such as diffusion barriers and abnormalities in pulmonary capillary circulation.

4. Inhaled insulin and upper respiratory tract infection. Although inhaled insulin is designed to reach the deepest regions of the lungs rather than be deposited in the upper airways, it is essential to know the effects of upper respiratory tract infection on pharmacokinetics and pharmacodynamics. McElduff et al[22] studied such effects in 20 healthy volunteers during episodes of spontaneous upper respiratory tract infection and after recuperation; they found no significant differences. Furthermore, the number and intensity of hypoglycemic events was similar in patients with type 1 and type 2 diabetes treated with inhaled insulin or subcutaneous insulin, regardless of presence of upper respiratory tract infection. We consider this observation important, given how common upper respiratory tract infections are in patients with diabetes.

It follows from that discussed above that inhaled insulin is contraindicated for active smokers or those who have smoked during the 6 months preceding treatment; patients with severe, unstable, or uncontrolled asthma; patients with stage III or IV COPD (according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification)[18]; and for children and pregnant women owing to a lack of clinical trials in these populations.

We believe that the few studies done in small patient populations do not allow definite conclusions to be drawn on the response to inhaled insulin in diabetic patients with associated lung disease and/or microvascular disease, and that broader-based, long-term studies are needed. Such studies will probably find that inhaled insulin administered preprandially may be an efficacious complement to basal insulin or semi-slow acting subcutaneous insulin in patients with type 1 diabetes under intensive treatment regimens, and in those with type 2 diabetes as a complement to treatment with oral antidiabetic drugs. Furthermore, inhaled insulin is well-tolerated by both types of diabetic patient.[5,6,23,25] Fewer injections mean less "servitude" to the disease and a better quality of life. This should lead to better treatment adherence, improved metabolic control, and probably to a reduction of morbidity and mortality related to metabolic and vascular complications.

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