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COMMENTARY

Inhaled Insulin: Take a Deep Breath, but How?

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Abstract

Inhalation of insulin is the first alternative route of insulin administration, which has been developed to such a mature status that the first product (Exubera®, Pfizer) was made available to the market and subsequently withdrawn as of early 2008. In view of the relatively low bioavailability of inhaled insulin and the intraindividual variability of the metabolic effect induced (which is in the range of that of subcutaneously applied regular insulin), one wonders how to improve both aspects. Unfortunately, it appears as if the impact of the inhalation maneuver on insulin deposition in the deep lung has not been studied extensively. We present some thoughts and data from an alveolar model and propose an experimental procedure that might be helpful in the quantitative evaluation of the impact of the insulin inhalation maneuver.

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Introduction

The first inhaled insulin preparation, Exubera, has been marketed in the United States and Europe for some time now by Pfizer for the treatment of patients with type 1 and type 2 diabetes. However, because of insufficient sales, it was withdrawn from the market as of early 2008. Other inhaled insulin preparations are likely to follow in the next few years. Despite quite comprehensive clinical development programs [involving more than 4600 patients in the case of Exubera (http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4169S1_00_Slide-Index.htm)], one relevant aspect seems to have been more or less ignored by the manufacturers of inhaled insulin: No published data (except in the format of abstracts) are available on the impact of different inhalation maneuvers on the efficacy of insulin deposition and the variability of the insulin action induced with Exubera. One small study with a different system (AERx; Aradigm/Novo Nordisk), published earlier, showed that the breathing technique changes the time to peak serum insulin levels, as well as the size of the peak.[1] This aspect has not been mentioned even in recent reviews about inhaled insulin![2]

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However, data from studies in environmental and radiation protection studies clearly show that the inhalation technique has a considerable impact on the deposition of particles in the deep lung.[3–10] In fact, the inhalation technique is much more critical for the metabolic efficacy than the particle size used. We used previously published data[5] to model alveolar deposition (relative to the emitted dose) of particles with the size of Exubera. An established model, the human respiratory tract model for radiological protection, was used for calculations. Mean relative alveolar deposition was approximately 25%, but differed by 770% between the best and the worst inhalation maneuvers (**Figure 1**). Moreover, this model also showed that when always using the same inhalation technique, changes in the particle size from 2 to 6 µm would only impact relative alveolar deposition by 56%.

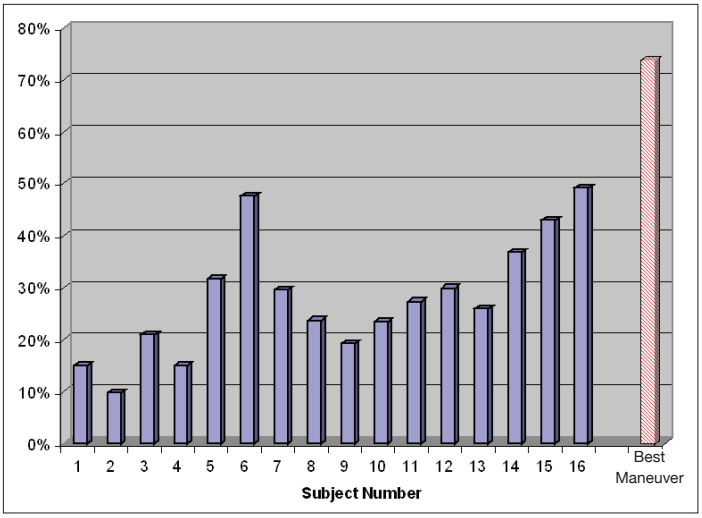

Figure 1. Relative alveolar deposition.

The optimal inhalation technique may vary considerably, depending on the inhaler technology and the particle size used. For instance, it is recommended to hold one's breath after the inhalation of small particles, but not necessarily after inhaling larger particles. For commercially available dry powder inhalers used for asthma and chronic obstructive pulmonary disease treatment, it is recommended to inhale fast, whereas optimal deposition with jet nebulizers is achieved with the slowest possible inhalation.

The insulin particles used by the different insulin inhalation systems on the market or in development differ in consistency, surface properties, and a number of other factors. In addition, the inhalers themselves differ considerably in their properties. Therefore, it seems questionable if the inhalation procedure optimal for one development is also the best procedure for all the other insulin particles and inhalers. It seems more likely that the maneuvers need to be optimized for each inhaler and for the individual particle properties.

A straightforward approach to evaluate the optimal inhalation technique might be the use of reference inhalers such as the AKITA system,[11–13] which allows specifically modifying and controlling the inhalation characteristics, e.g., inhalation flow rate, inhalation volume, and inhalation time (http://www.activaero.de/dateien/akita-presentation-e-700.pdf). The AKITA is a bedside inhalation system that also controls compliance and medication dose. It allows full electronic control over a patient's inspiration. The usage of such a system should allow a reproducible application of insulin in the deep lung. Combining the control of the inhalation maneuver through such an inhaler with a highly standardized assessment of the metabolic effect of an inhaled insulin formulation with the glucose clamp technique would be a relatively simple and straightforward approach to optimize the inhalation procedure. This could also be used to investigate other important aspects of the inhalation procedure, such as the impact of a breath-hold period after inhalation on the induced metabolic effect/biopotency. Finally, by repeated assessments it may be possible to study and eventually minimize the intraindividual variability of the induced metabolic effect just by optimizing and standardizing the inhalation maneuver.

However, not only is the inhalation maneuver important, but also the moment of insulin release during inhalation. It seems easily conceivable that the inhalation flow rate and the inhalation volume at and after insulin release might have profound impacts on the delivery of insulin particles into the alveoli.

By optimizing the inhalation technique, it might be very well feasible to improve the bioavailability of inhaled insulin formulations. The currently reported, relatively low bioavailability of about 10% for Exubera[14] certainly is an economic challenge, which has led to recommendations of health care institutions to further evaluate the clinical and cost-effectiveness of inhaled insulin in clinical studies prior to usage in the routine treatment of people with diabetes.[15] Furthermore, if patients are well trained in the optimal inhalation technique (or if the inhaler only allows minimal variations in the inhalation procedure), it might be possible to reduce the within-subject variability in the elicited metabolic effect, which currently

is in the same high range as that of subcutaneously applied regular human insulin (reported coefficient of variations are mostly in the range of 20–30%[16]).

Once the optimal inhalation procedure is determined for a given inhaled insulin development, it will still be a challenge to ensure that patients (preferably all the patients) apply this procedure under daily life conditions. Not without reason was patient education one of the major topics discussed during the Exubera Food and Drug Administration advisory board meeting. Unless the inhaler really guides patients through the optimal inhalation technique, the variability in the inhalation procedure might be excessive, despite potentially detailed instructions and extensive education. Patients must at least know about the impact of different inhalation techniques on the variability of the induced metabolic effects to be aware of potential under- or overdosing. However, a good (yet sad) example of how well patients can learn to optimize their inhalation technique is through hard "training." Many smokers manage to maximize the absorption of nicotine (even if the cigarettes contain a relatively low amount of nicotine) by an improved inhalation technique.

In conclusion, a more in-depth assessment of the optimal inhalation technique appears to be necessary to further improve the metabolic profile and/or the biopotency of inhaled insulin. A higher reproducibility is of critical importance in achieving a broader acceptance of this novel route of insulin administration and in finally promoting inhaled insulin from a mere convenience drug to a major improvement for patients with diabetes.

Disclosure:

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