

INHALABLE INSULIN: THE BREAKTHROUGH IN INSULIN THERAPY?

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Recent reports suggest an almost epidemic nature in the incidence of diabetes mellitus in the first decades of the 21st century. Far from being only a widespread disease in the “developed” countries, diabetes may become a global burden. A study linking data from a global database collected by the WHO with projections and demographic estimates of the United Nations expects a worldwide increase in the number of adult patients with diabetes, from 135 million in 1995 to 300 million in the year 2025. The study suggests that for the whole world, the adult population (>20 years) will increase by 64% between 1995 and 2025, thus the prevalence of diabetes in adults will increase by 35% and the number of people with diabetes will increase by 122%.¹ The highest increase in the prevalence of diabetes is estimated to occur in China (68%) and India (59%).

The Middle East region may experience a 30% increase in the prevalence of diabetes. It is estimated that in 2025, Egypt may be among the 10 “leading” countries in the world in terms of the number of people with diabetes.² Data derived from the Arabian peninsula (Oman, Saudi Arabia), countries already showing a high prevalence of diabetes mellitus,^{3,4} suggest an alarming increase in the incidence of the condition. The problem has been well documented in Saudi Arabia, and concerns type 1 diabetes,⁵ as well as type 2 diabetes in urban and in rural areas.⁶⁻⁸ The problem goes hand in hand with an increasing number of obese people in the Arabian peninsula (about 30%),^{9,10} where obesity is rising steadily, especially among women.¹⁰

Since there are no really efficient or practicable methods to prevent the manifestation of types 1 and 2 diabetes in the population as a whole, emphasis has to be laid on adequate and effective therapy to preserve patients’ fitness for work, and prevent late sequelae of the disease. Without any doubt, the development of inhalable insulin is among the most interesting new therapeutical approaches.

Materials and Methods

The idea of the application of insulin in an inhalable form was first published in 1925,¹¹ and has led to

encouraging results in the recent years.^{12,13} This concept holds a lot of potential advantages in comparison to the current subcutaneous injection of insulin:

- Current data suggest that inhalable insulin has a faster mode of action, almost comparable to the rapid-acting insulin analogues, and it also clears faster than regular insulin.¹⁴⁻¹⁷
- Inhalable insulin enables patients to escape the sometimes painful injection, and may allow an earlier onset of insulin therapy in many cases.
- Since regular insulin does not have to be injected by needles, there is no more risk of infection by contaminated needles for the medical staff.

At the 60th Annual Meeting of the American Diabetes Association in June 2000, data from six companies developing inhalable insulin were presented.^{14,18-22} The concepts and techniques of the two most advanced developments are presented here in detail.

In cooperation with two “global players” (Aventis™ and Pfitzer™), Inhale™ has developed a new dry powder insulin formulation, together with a special delivery system that allows reproducible dosing of insulin by inhalation. The insulin powder is kept in an amorphous state and is presumably stabilized by manitol and glycine. There is no need to add absorption enhancers, which had caused a lot of problems (nasal irritation, allergic reactions) in former trials, to develop an insulin formulation to be delivered as a nasal spray. The exact production process is still a secret of Inhale™. The insulin powder is packed into blisters with different dosages. The present studies were performed with blisters containing 1 or 3 mg of insulin powder, equivalent to about 3.3 or 10 IU of conventional subcutaneously injected insulin.^{18,23,24} A special aerosol delivery system generates a pulse of compressed air, thus deagglomerating the dry powder insulin into a white cloud and delivering it from the blisters into a transparent reservoir, from where it is to be inhaled, ideally in one deep breath (Figure 1). Since the particles have a size of 1-3 μm, they can reach the alveoles without clotting in the bronchi. The alveolar surface in a healthy human being is almost the size of a football field (approximately 70-100 m²). It is capable of absorbing about 30% of the insulin inhaled by “transcytosis,” and the remaining 70% is considered to be decomposed by local proteolysis.

Many patients significantly favor inhalable insulin, in comparison with subcutaneous injection, although the inhalation devices are still quite bulky.^{18,20} However, up to now, only prototypes have been used and the final design of

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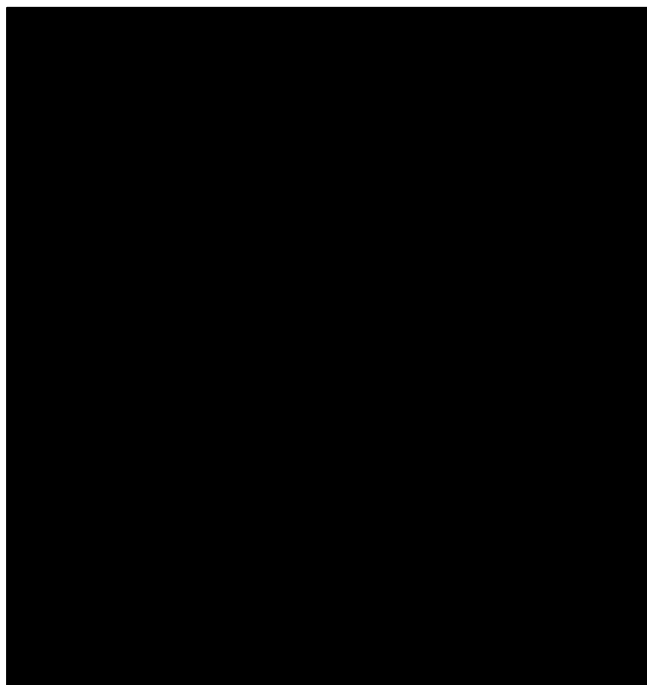


FIGURE 1. Schematic diagram of the presently most advanced inhalation device (Inhale™).

TABLE 1. Data derived from three-month, multicenter clinical phase II trials in type 1¹⁶ and type 2 diabetics.²⁵

| Type of diabetes and mode of treatment | HbA _{1c} (start of study) | HbA _{1c} (3 months after start of study) |
|--|------------------------------------|---|
| Type 1 (n=35) | | |
| 2-3 Subcutaneous injections/day | 8.5 ± 1.1% | 7.7 ± 0.9 % |
| INH+bedtime Ultralente | 8.5 ± 1.1% | 7.9 ± 1.0% |
| Type 2 (n=33) | | |
| OA | 9.9 ± 1.3% | 9.8 ± 1.2% |
| INH ± OA | 9.8 ± 1.3% | 7.6 ± 1.3% |

Inhaled insulin is as effective as subcutaneous injections in type 1 diabetics and significantly improves glycemic control ($P < 0.0001$) if added to OA in type 2 diabetics; data given as mean ± SD; OA=oral antidiabetics; INH=inhaled insulin.

the device is expected to be smaller and easier to handle. Inhalable insulin seems to be a useful alternative to injections in both type 1 and 2 diabetics. Since the kinetics of inhalable insulin are comparable to those of regular insulin, NPH insulin must still be injected additionally in both groups of patients. In type 2 diabetics, a combination therapy with oral antidiabetic drugs can improve glycemic control.²⁵ Since the present blisters do not allow for a large variety of individual dosings, as would be necessary, e.g., in children, the main target group for the inhalable insulin has been type 2 diabetics up to now. Still, most clinical trials with this inhalable insulin have been published as abstracts only. A large-scale multicenter phase III study was recently started.

Another competitor in the race for marketing inhalable insulin is actually represented by Novo™ in cooperation with Aradigm™. Their system is based on an inhaled

aqueous formulation of insulin delivered by a special inhalation device (AERx™ Diabetes Management System). Since the problems in the correct handling of classic inhalation devices by the patients are well known from their use, e.g., in the treatment of pulmonary diseases such as asthma or chronic bronchitis, the AERx™ Diabetes Management System was designed to meet the special needs for exact dosing of inhalable insulin. This system generates a low-velocity aerosol consisting of very small particles. Thus, oropharyngeal deposition is greatly reduced, which otherwise accounts for a major source of variability of drug delivery to the lungs. The aerosol is generated from an aqueous formulation, using a special disposable nozzle containing an array of micromachined holes. The patient's inspiratory flow is monitored by the device and the aerosol is instantaneously generated for inhalation when a predefined optimum inspiratory volume and flow rate is achieved by the patient. The internal microelectronic system guides the patient by optical feedback.²⁶ In this system, no absorption enhancers are added to the liquid insulin formulation. The aerosol bolus insulin also shows a faster absorption and a more rapid onset of metabolic effects when compared to subcutaneously injected insulin.¹⁴ Several phase II studies are expected soon, but currently most data are available as abstracts only.

The developments of Lilly/Dura, Becton-Dickinson/Aerogen,¹⁹ Alkermes/Air Development,²¹ and Pharmaceutical Discovery Corporation^{15,22,17} actually seem to represent earlier states in the development of systems for inhalable insulins. Interestingly, in the case of the AIR insulin, the company develops both fast-acting and slow-acting inhalable insulin formulations.²¹ A completely different approach is presented by Generex™. A liquid formulation of insulin is delivered into the mouth as an aerosol, using a specially designed device (Rapid Mist™). The aerosol particles are highly accelerated to ensure a high oropharyngeal deposition. The particular formulation of the insulin allows the drug molecules to traverse the oropharyngeal mucosa. Clinical phase II studies are expected soon, but detailed data are not yet available.

Discussion

The discomfort associated with subcutaneous injection therapy and patients' fear of self-injection still remain some of the main problems in initiating an insulin therapy. In the search for an alternative route of insulin administration, the intranasal application of aerosolized insulin led to disappointing results, as well as the oral delivery of insulin within capsules or pills. In contrast, the application of insulin by oral inhalation shows promising results. The bronchopulmonary system is obviously able to absorb insulin in a dose-dependent and reproducible manner, thus being as effective as subcutaneous insulin injections in type 1 diabetics, and significantly improving glycemic control in type 2 diabetics if added to oral antidiabetic drugs (Table 1). The inhalation procedure sometimes causes some

coughing, but usually the procedure is well tolerated by the patients.^{18,20}

Before a large-scale introduction of inhalable insulin onto the market, some major points should be carefully investigated. First, the main concerns of many researchers are the uncertain long-term effects of the intra-alveolar deposition of insulin. It is well known that insulin has growth-promoting properties,²⁷ but its long-term effects on the pulmonary connective tissue are unknown. To date, serial pulmonary function tests have not shown any significant changes in the parameters of lung function, but these data are still based on limited experience of not more than two years. Up to now, there have been no clinical data indicating increased cellular proliferation or even promotion of tumor growth. Second, as a rule of thumb, inhalable insulin has to be applied in an 8-9 fold dose to achieve the same glucose-lowering effect of subcutaneous injection. This may lead to significantly higher therapeutic costs, but manufacturers have not yet commented on this aspect. Third, the high dose of insulin delivered to the lungs theoretically may cause immune responses, e.g., formation of anti-insulin antibodies. This aspect seems to be less important, because with regards to immune response, the subcutaneous compartment is a much more reactive site than the lung, which is relatively immune tolerant. Since human insulin is used for inhalation, the incidence of anti-insulin antibodies can be expected to be similar or even less than during subcutaneous injection, which is known to be very low.²⁸ Nevertheless, this aspect should be addressed during further trials. Fourth, since patients with concomitant bronchopulmonary disease have been excluded from recent studies on inhalable insulin, there are no data on the pharmacokinetics of inhaled insulin in these patients as yet. On a theoretical basis, one might expect that many conditions affecting the bronchopulmonary system could interfere either with the alveolar deposition of inhaled insulin or with its resorption from the alveoli. Even a simple cold or an acute bronchitis could be expected to affect the pharmacokinetics of inhaled insulin. Today, little is known about the use of inhalable insulin in patients with asthma, emphysema or chronic obstructive pulmonary disease (COPD). On the other hand, in active smokers without apparent bronchopulmonary disease, the absorption of inhalable insulin is sometimes even faster and stronger. These aspects must be addressed in detail before inhalable insulin could be used in these patients on a routine basis.

To summarize, a number of recent studies have demonstrated that the use of inhalable insulin may offer distinct advantages to the diabetic patient, e.g., in terms of faster mode of action when compared to subcutaneously injected insulin. Another major advantage is the painless mode of application, representing a superior approach, in comparison to jet injection devices that may cause less pain than the subcutaneous injection, but are still not completely pain-free. However, as mentioned, some problems still have to be solved and other potential limitations carefully investigated. Hopefully, the current race for the leadership position in the growing global market of diabetes therapy

will not prevent the manufacturers from pursuing a careful and conscientious investigation into these problems. As well, the pressure of competition may keep these new techniques from becoming too expensive, thus helping to improve glycemic control and quality of life for diabetics in the whole world.

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