# Review: Current status of the development of inhaled insulin

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# Current status of the development of inhaled insulin

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## Abstract

**The most promising alternative route of insulin administration seems to be pulmonary delivery by inhalation. For a maximal rate of absorption insulin must be applied deep into the lung, i.e., into the alveoli. A number of inhalers designed to generate an aerosol with an appropriate particle size for pulmonary delivery are currently in clinical development. The pharmacodynamic effects of insulin formulations administered via the lung are comparable to, or are even faster than, those of subcutaneously injected regular insulin or rapid-acting insulin analogues. The relative biopotency of inhaled insulin is approximately 10%, i.e., the dose of inhaled insulin must be 10 times higher than the dose applied subcutaneously in order to induce a comparable metabolic effect. Clinical trials indicate that metabolic control with this pain free route of insulin administration is at least comparable to that of subcutaneous (sc) insulin therapy. Side effects observed in human trials, gave rise to safety concerns that have delayed development for several years. Nevertheless, recent long-term safety studies indicate that the increased stimulation of insulin antibody formation stopped after some time and that the observed changes in lung function were minor or reversible. Consequently the first application for an approval of pulmonary insulin has been submitted to the authorities. In summary, it seems as if, after several decades of research, for the first time a feasible alternative route for insulin administration is within reach.**


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**Key words:** inhaled/inhalative insulin, inhalers, alternative route of insulin administration, lung, risks, bioavailability, biopotency, variability, diabetes.

## Introduction

For the past 80 years sc injection has been the only route of delivering insulin to patients with diabetes mellitus. However, sc insulin administration does not lead to optimal pharmacodynamic properties of the applied insulin; absorption into the blood stream (even with rapid-acting insulin analogues) is not that rapid, so that a precise mimicking of the prandial physiological insulin secretion pattern is not possible. Immediately after the discovery of insulin and in the decades thereafter, a variety of routes of administration have been investigated for their applicability, mainly in order to reduce the pain associated with sc injection and in order to improve the pharmacodynamic properties of the applied insulin.

The alternative routes of insulin administration which have been studied in great detail for their clinical applicability include dermal, oral, nasal and pulmonary routes.[1] Dermal insulin application does not result in a reproducible and sufficient transfer of insulin across the highly efficient skin barrier. The dream of an 'insulin tablet' has also not become reality, the main problem being digestion and a lack of a specific peptide carrier system in the gut. Nasal insulin application led to a rapid absorption of insulin across the nasal mucosa; however, the relative bioavailability was low and required the use of absorption enhancers. To date, it appears that the pulmonary application of insulin is likely to be the first alternative route of insulin administration to become available within the next few years.

## Basic considerations

The lung has inherent advantages for insulin administration. These include: a vast (in humans 50–140 $m^2$, ~500 millions of alveoli) and well-perfused absorptive surface (~5 L blood/min, pulmonary capillary blood volume ~0.25 L), the absence of certain peptidases which are present in the gastrointestinal tract, no immediate degradation of the absorbed insulin by the liver ('first pass metabolism'), and a thin alveolar-capillary barrier.[2] These conditions allow a fast absorption of peptides into the bloodstream and a rapid onset of action after inhalation, i.e., the lung represents a highly permeable 'port of entry' into the blood for macromolecules.[3]

For a maximal absorption rate insulin must be applied deep into the alveoli. Only particles with a size < 10 µm are transported into the finer bronchial branches and alveoli with the airflow. Larger particles precipitate on the mucous membranes of the mouth and pharynx or on the larger bronchial branches. Particles with a size < 1 µm will not be deposited on the mucous membranes in the airways, but will be exhaled. The optimal particle size for pulmonary insulin administration appears to be in the range of 2–5 µm. The insulin particles which are deposited in the

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**Abbreviations**

| | |
|---|---|
| DLCO | carbon monoxide diffusing capacity |
| GIR | glucose infusion rates |
| GLP-I | glucagon like peptide |
| $HbA_{1C}$ | haemoglobin $A_{1C}$ |
| MDI | metered dose inhaler |
| NPH | neutral protamine Hagedorn |
| PDC | pharmaceutical discovery cooperation |
| sc | subcutaneous |

alveoli are assumed to be rapidly dissolved in the thin mucous liquid film covering the inner surface of the alveoli.

An aerosol with an appropriate particle size distribution can be obtained by the nebulisation of an insulin solution (= mist) or by the pulverisation of solid insulin particles (= smoke). Another approach is to use large porous particles (developed by AIR/Alkermes) with low density (< 0.1 g/cm$^2$) for inhalation.[4] Due to their low particle mass density, these particles have a large geometric (10–20 µm) but a small aerodynamic diameter (1–3 µm). Others also use artificial particles (Technospheres™/ Insulin; see below) as the drug carrier.[5,6] One advantage of these artificial particles is their highly uniform size.

## Bioavailability/biopotency

Insulin in a given aerosol (independent from powder or liquid) is unevenly distributed among particles with various sizes and deposition properties. Thus, the inhalation of insulin cannot be expected to yield 100% of the applied dose. Several studies with inhaled insulin showed a relative bioavailability/ biopotency of approximately 10%. The reasons for the loss of 90% of insulin during inhalation are not fully understood:

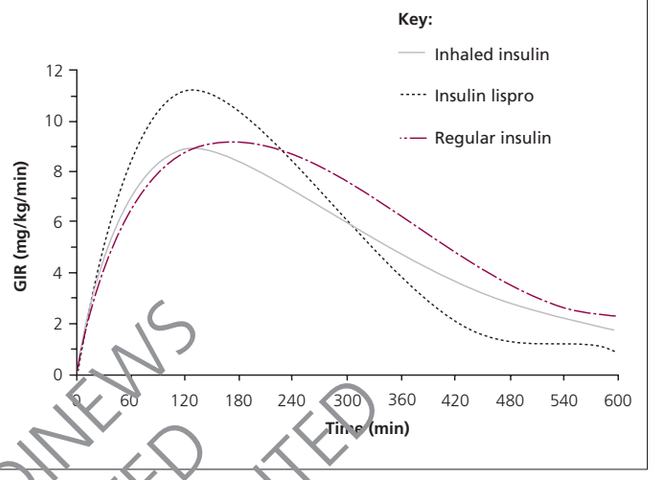
1. Part of the insulin remains in the (drug) container after inhalation,
2. Part adheres to the inner surfaces of the inhaler,
3. Larger particles (containing a lot of insulin) are deposited in the mouth, throat and bronchial tree
4. Smaller particles are exhaled without being deposited,
5. Insulin deposited in the alveoli is degraded by macrophages and peptidases.

## Clinical-experimental studies and status of the development

It was the invention of modern handheld inhalers, allowing the generation of an aerosol with an adequate particle size distribution, some 15 years ago, which started the rapid development of pulmonary insulin administration. A considerable number of inhalers differing in construction, size, weight, handling, etc. are currently in the clinical phase of development.

In the first study investigating the time-action profile of a pure dry powder insulin preparation (99 IU), inhaled with a small inhaler was employed in a glucose-clamp study in healthy male volunteers. It showed that the onset of action was more rapid than that of sc regular insulin and the duration of action comparable.[7] The addition of an absorption enhancer (a bile salt) led to considerable changes in the time-action profile of the inhaled insulin powder aerosol, i.e., the onset of action was substantially more rapid than with the previous formulation without enhancer, and the metabolic effect in the first two hours after inhalation was significantly greater.[8] The observed effect was comparable to, or even better than, that reported with rapid-acting insulin analogues, but the decline in metabolic activity seemed to be slower. This study also showed that the intra-individual variability with inhaled insulin was nearly identical with those after sc injection of regular insulin.

**Figure 1.** Mean glucose infusion rates (GIR) registered in 17 healthy subjects after inhalation of 165 IU insulin, sc injection of 18 IU regular insulin and sc injection of 18 IU insulin lispro. A polynomial function of 6th order was fitted to the raw data[9]




The time-action profiles obtained in healthy subjects with inhalation of 6 mg insulin via the dry powder inhaler system Exubera® (being developed by Pfizer Inc. and Aventis Pharma in conjunction with Nektar Therapeutics), were compared with those of sc injection of the rapid-acting insulin analogue insulin lispro and of regular insulin (both 18 U). The comparison showed that the onset of action with the inhaled insulin powder was even more rapid than that of the rapid-acting insulin analogue (figure 1).[9] Maximal metabolic activity was lower than that of insulin lispro, but comparable to that of regular insulin, i.e., 1 mg inhaled insulin corresponded to 3 IU sc regular insulin. The duration of action was intermediate between that of the two sc administered insulin preparations. The relative biopotency was 10±4% (*vs.* regular insulin) and 11±4% (*vs.* lispro). This inhaler is the most advanced product in terms of clinical development, after the phase III trials and additional safety trials have been performed (see below) this system is now in the approval process.

Insulin administered as an aerosol via the inhaler AERx (produced by the company Aradigm, Hayward, CA, US) with four different insulin doses (0.3–1.8 U/kg) to the lung of patients with type 1 diabetes showed a linear dose-response relationship of

pharmacokinetic and pharmacodynamic parameters in a glucose-clamp study.[10] The relative biopotency over six hours was 13%. In a clinical-experimental study with the AERx inhaler nonsmoking subjects with type 1 diabetes inhaled the same dose of insulin on four study days (n=9) or received a sc insulin injection.[11] Thereafter they ate a standardised test meal. Serum insulin excursions and blood glucose changes in the six hours showed similar or lower intra-individual variability of certain pharmacokinetic and pharmacodynamic summary measures compared to sc insulin administration. This confirms the reproducibility of insulin administration for prandial insulin therapy. The AERx inhaler is currently in phase III trials and is probably the second one which will come to the market.

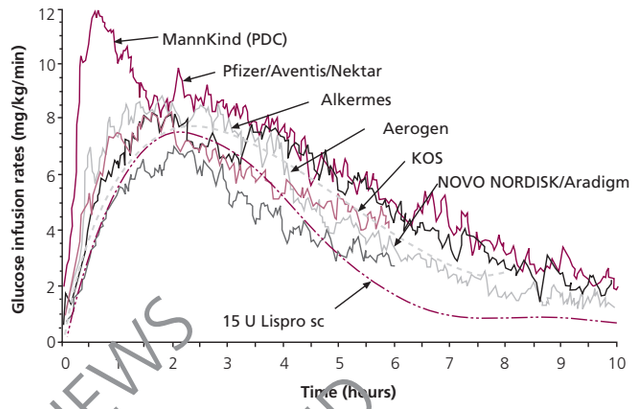
The pharmacodynamic properties of Technospheres/Insulin (MannKind [former PDC; Valencia, CA, USA]) showed a much more rapid onset of action than after sc administration of regular insulin.[6] Moreover, the relative biopotency over six hours of the inhaled insulin (19±7%) was nearly twice as high as the biopotency observed with other insulin formulations/inhalers. A dose-response study with healthy volunteers who inhaled three different doses (25, 50 and 100 IU) showed a stepwise, dose-dependent increase in metabolic activity.[12] The peak metabolic effect was registered two hours earlier than with sc regular insulin. The variability in the metabolic response in 12 patients with type 2 diabetes after the inhalation of 100 IU insulin was also within the range observed with sc regular insulin in healthy volunteers.[13] After some years of rapid development performance of phase II trials was delayed for a while, however, they are currently being performed.

Use of large porous particles loaded with insulin, which are stable at room temperature, allows Alkermes (Cambridge, MA, USA) in cooperation with Eli Lilly (Indianapolis, IN, USA) to construct small, elegant inhalers. Clinical-experimental studies performed with this approach showed that inhalation of 84, 168 and 294 IU by means of this powder-based system induced a fast onset of action in comparison to sc regular insulin and a linear dose-response, with a biopotency of 18%.[14] This system is currently in phase II trials.

The inhalation of a commercially available U500 formulation of regular insulin (Humulin R, Eli Lilly, Indianapolis, IN, USA) with an inhaler developed by Aerogen (Mountain View, CA, USA) resulted in an earlier maximal metabolic effect than with sc insulin injection in healthy subjects.[15] From the two aerosol particle sizes studied (3.5 *vs.* 4.4 µm) and the two aerosolisation times (2 s *vs.* 4 s) studied, the impact of the aerosolisation time on the metabolic effect induced was higher than the difference in the particle sizes. Only phase I studies have been performed with this system so far and it is not clear when development will continue to the next phases.

The company KOS (Miami Lakes, FL, USA) has developed a novel regular insulin preparation which is applied to the lungs with a simple, inexpensive, and strictly mechanically working metered-dose inhaler (MDI). That means, there are no electronic controls governing the operation of the device. Inherent in such a mechanically oriented design are robustness and reliability. In a glucose clamp study with healthy subjects inhalation of three different insulin doses (45, 89 and 134 U) induced a rapid onset of action in comparison to sc injection or 10 IU regular insulin and a linear dose-response relationship.[16] Biopotency ranges between 10 and 15% compared to sc regular insulin. Currently the first small phase II studies with this inhaler have been started.

**Figure 2.** Composite figure with the time-action profiles obtained with a variety of inhalers from different manufacturers in different studies

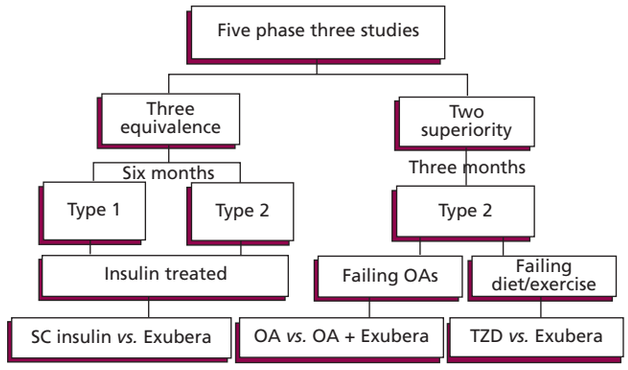



The inhalation of insulin particles results in a time-action profile which is characterised by a faster onset of action than with sc regular insulin and by a duration of action which seems to be intermediate between that of sc rapid-acting insulin analogues and sc regular insulin. Figure 2 shows that such a time-action profile was observed with nearly all inhalers that are currently under development. The mean curves presented in this diagram were obtained in different studies (with different doses, however, all in healthy subjects). The similarity of the profiles (with the exception of the MannKind development [former PDC] which has a more rapid onset of action), indicated that after application of insulin into the peripheral lung a more or less uniform metabolic effect can be expected. There is an ongoing debate whether powder insulin or a liquid inhaled insulin formulation is better in terms of reproducibility, aerosol quality, shelf-life etc. However, as long as no direct comparative clinical-experimental and clinical studies have been performed, it is difficult to make a definitive statement.

## Clinical trials

The published data about the results of the phase III trials (figure 3) with Exubera indicate that the metabolic control achieved is superior compared to oral agents and comparable to sc insulin. This inhaled insulin controls fasting blood glucose more effectively than oral agents or sc insulin. In these trials Exubera was well tolerated during long-term use, with no increased risk of hypoglycaemia and was preferred by the patients over sc insulin

**Figure 3.** Overview of the Exubera Phase III program




**Key:** OA = oral agent; TZD = thiazolidinediones

and oral agents. The phase III results confirms the results of the phase II trials.[17-20] Like in the phase II trials, patient's satisfaction was enhanced with inhaled insulin treatment compared with sc insulin injections.[21]

In a 24-week multicentre phase III study, involving subjects with type 1 diabetes, treatment with pre-meal inhaled insulin plus a morning and a bedtime injection of NPH insulin (n=163) was compared to treatment with a regular sc insulin prior to meals plus twice NPH insulin per day.[22] Subjects in the inhaled insulin group achieved comparable changes in $HbA_{1C}$ (-0.3%) to those in the sc group (-0.1%). Fasting blood glucose was lower with inhaled insulin; however, the two-hour postprandial glucose levels and the incidence of hypoglycaemic events were comparable in both groups. In another 24-week multicentre phase III study, involving in total 334 subjects with type 1 diabetes, treatment with pre-meal inhaled insulin plus a single bedtime injection of ultralente was compared to treatment with a conventional sc insulin regimen consisting of two to three injections of regular/NPH insulin per day. Again subjects in the inhaled insulin group achieved comparable changes in $HbA_{1C}$ to those in the conventional sc group (-0.2 *vs.* -0.4%;[23]).

Six months treatment of patients with type 2 diabetes by means of inhaled insulin plus a single bedtime injection of ultralente (n=149) compared to two injections of sc insulin (mixture of regular/NPH insulin; n=150) resulted in a similar decline in $HbA_{1C}$ (-0.7 *vs.* -0.6%).[24] Another study with patients with type 2 diabetes who where inadequately controlled on oral hypoglycaemic agents showed that those receiving inhaled insulin monotherapy (n=105) or inhaled insulin combined with an oral agent (n=102) achieved greater improvement in $HbA_{1C}$ (-1.4% and -1.5% *vs.* -0.2% respectively) than those on oral agent therapy alone (n=102).[25] Pre-meal inhaled insulin administration also resulted in better glycaemic control in 145 patients with type 2 diabetes than treatment with an insulin sensitiser.

In a phase II trial with the AERx inhaler glycaemic control was evaluated for 12 weeks in insulin-treated patients with type 2 diabetes.[26] One group of patients (n=47) inhaled insulin prior to each meal, the other group (n=49) injected regular insulin sc prior to each meal. Patients in both groups received NPH-insulin at bedtime only. The metabolic control achieved was comparable at the end of the study (7.8 *vs.* 7.8%; Inhaled *vs.* sc). However, as in the studies with Exubera the fasting blood glucose was lower with inhaled insulin in this study (8.9 *vs.* 10.8 mmol/L; p=0.01). The prandial insulin dose was higher with inhaled insulin than with sc insulin (0.40 *vs.* 0.34 IU/kg); the basal insulin dose was comparable. The incidence of hypoglycaemic events was comparable with both routes of insulin administration. Also no other side effects, for example changes in lung function, were observed.

## Costs of therapy with inhaled insulin

A relative bioavailability/biopotency of 10% implies that a 10x greater amount of insulin has to be given in order to achieve a metabolic effect comparable to that of sc administered insulin. Therefore, the cost of inhaled insulin therapy is higher than that of sc insulin therapy. One issue with the different developments described above is that the insulin doses these are declared to deliver are described differently. One company reports the amount given in milligrammes (it is unclear whether this refers to pure insulin or the final formulation which contains different amounts of excipients), one reports in microgramme, and others report in self-defined units. Due to the fact that no common standard is used, it is difficult to compare the metabolic effects induced by the applied insulin doses. Nevertheless, in view of the losses of insulin with inhaled insulin (see above), at the end the dose must be titrated until a sufficient metabolic effect can be achieved in a given patient, as is the case with all routes of insulin administration.

In view of the limited bioavailability/biopotency the crucial question is: Are the benefits of pulmonary insulin high enough to justify the expenses for this novel route of insulin administration, when sc insulin injection, a safe and well-established route of administration, is available? To answer this question, the following benefits of the pulmonary application of insulin over the sc have to be shown:

1. Improvement in metabolic control,
2. Reduction in the frequency of hypoglycaemic events, and
3. Better quality of life.

One of the major arguments in favour of inhaled insulin is the convenience of application. However, it is an open question which groups of patients will prefer this type of insulin administration: insulin naïve patients with type 2 diabetes, or those failing oral therapy? Depending on the inhaler used, it may be that for patients with type 1 diabetes dose adjustment is not possible in small enough steps. Also these patients are younger, and they might be more concerned with long-term side effects of inhaled insulin.

The idea is that the chance of avoiding regular injections is very attractive for the large number of type 2 diabetic patients who are reluctant to switch to insulin. Many of these patients

have poor metabolic control with their current treatment strategy. In easing the decision to switch to insulin treatment, and to thereby improve the metabolic control of this often neglected group of diabetic patients, lays one of the most attractive potentials for the application of inhaled insulin. Would more of these patients switch to insulin treatment at an earlier stage (= better metabolic control and lower incidence of diabetic complications)? Many costs could be saved, especially those related to the treatment of secondary complications. This could finally outweigh the additional costs for the insulin treatment.

In a recent study the potential availability of inhaled insulin on patient acceptance of insulin therapy was studied.[27] Patients with type 2 diabetes failing on diet or oral therapy ($HbA_{1C} \geq 8\%$) were randomised to two groups. Both groups (A and B) received information about currently available treatment options; Group B also received material about Exubera as another potential treatment. Subjects were then asked to make a choice of diabetes therapy, including no change in their current treatment. The primary outcome was the proportion of patients choosing insulin. In total, 779 patients (A=388, B=391) were recruited in seven countries (Canada, France, Germany, Italy, Spain, Sweden, USA). In Group B, 169 patients (43.2%) chose a treatment option that included insulin compared with 60 (15.5%) in Group A (odds ratio 4.16, 95% CI [2.93, 5.95], p<0.0001). Amongst options in Group B, Exubera was most frequently chosen (35.3%). It was concluded that the availability of inhaled insulin as a potential treatment may increase willingness to change from failing treatments to more appropriate therapy including insulin.

## Metabolic effects of inhaled insulin in smokers and patients with asthma

It was already known, that inhalation of insulin by smokers induced a more rapid and larger increase in serum insulin levels compared to non-smokers, most probably due to smoking increasing the permeability of the alveolar-capillary barrier.[28] However, a recently published pharmacokinetic study investigated for the first time whether acute smoking in comparison to chronic smoking in 23 non-diabetic smokers resulted in a different absorption of pulmonary applied insulin.[29] On one study day smokers (n=23) smoked three cigarettes immediately before inhaling a small insulin dose of 34 IU by means of the AERx inhaler, on the other study day they had not smoked for nine hours. Absorption of inhaled insulin was greater in the smokers compared to the 13 non-smokers; the maximal exogenous insulin levels were approximately three times higher! Maximal values tend to be lower after acute smoking, probably because the smooth muscles of the airways were constricted. Interestingly no differences in the blood glucose lowering effect were observed between acute and chronic smoking.

Higher serum insulin concentrations in smokers must not necessarily result in a greater metabolic effect, as smoking patients tend to be more resistant to the metabolic effects of insulin. Unfortunately, only changes in blood glucose were evaluated in this study.

In a similar pharmacokinetic study with 16 non-diabetic, non-smoking patients with mild-to-moderate asthma an identical dose of 45 IU was inhaled via the AERx inhaler on two study days and a dose of 135 IU on the third study day.[30] In comparison to 28 healthy subjects the area under serum insulin profiles was significantly smaller for patients with asthma, i.e. they absorb less insulin via the lung. Also the high insulin dose applied showed no effects on pulmonary function/airway reactivity. The conclusion for this study was that patients with diabetes and asthma probably have to inhale more insulin to achieve good metabolic control. Another clinical-experimental study with this inhaler has shown that upper respiratory tract infections in 10 subjects without diabetes did not seem to induce clinically relevant changes in the pharmacokinetic responses to six AERx units of inhaled insulin.[31]

## Potential risks associated with the inhalation of insulin

In phase II and III studies with Exubera insulin antibody formation was evaluated. Patients with either type 1 or type 2 diabetes experienced a rise in insulin antibody levels rapidly after switching to inhaled insulin. After six months of therapy the percentage of insulin antibody levels (median values; two different studies with type 1 patients) were[22]:

| | Inhaled insulin | sc insulin |
|---|---|---|
| Type 1 | 28 | 4 |
| Type 1 | 29 | 3 |
| Type 2 | 5.0 | 1.5 |

In the patients who stayed on sc insulin administration, no change in insulin antibody levels was observed. The increase was higher in patients with type 1 than with type 2 diabetes. It appears as if the largest increase in insulin antibody levels occur in the first months of treatment with inhaled insulin. However, detailed analysis of clinical data from the patients in these studies showed no correlation of antibody levels with increased glycated haemoglobin, insulin doses, or hypoglycaemia rates. Thus, the appearance of insulin binding antibodies appears not to be correlated to indices of metabolic control and clinical safety.

Also in phase II studies with inhaled liquid insulin (Exubera is dry powder insulin) increases in the level of insulin antibodies from baseline levels of 6% to 35% was observed with inhaled insulin, but remained unchanged in the patients with sc insulin therapy (10 to 9%).[26] Again in this study no correlation between changes in insulin antibody levels and metabolic control or insulin dose could be observed. However, that liquid insulin also induced insulin antibody formation shows that this is independent of insulin status, i.e. be it dry powder or a liquid.

The results of specific long-term studies on the development of insulin antibodies have reduced concerns about a clinically relevant effect of such antibodies.

Alterations in lung function were observed in some studies. For example a significant decrease in the carbon monoxide diffusion capacity (DLCO [ml/min/mmHg], changes from baseline)

relative to sc insulin was reported in phase III trials with the Exubera inhaler after six months of therapy in patients with type 1 and in type 2 diabetes as noted below[22-24]:

| | Inhaled insulin | sc insulin | 95% confidence intervals |
|---|---|---|---|
| Type 1 | - 0.750 | 0.229 | -1.49;-0.15 |
| Type 1 | -1.688 | -0.389 | -2.03;-0.58 |
| Type 2 | -1.046 | -0.385 | -1.57;-0.04 |

In further studies specifically designed to characterise these changes, the observed worsening of lung function seem to be reversible or temporary. Also in a relatively short study with type 2 diabetic patients using the AERx inhaler no differences in lung function (also in DLCO) were observed in the 12-week period.[26]

Local effects of inhaled insulin inside the lung, which might be present at relatively high concentrations at given locations in the peripheral lung where insulin particles are deposited, on vasodilatory/vasoconstrictory responses of the vessels in these areas are of potential concern. However, respective data obtained in an *in vitro* model with rat pulmonary arteries must be confirmed in appropriate studies in humans.[32]

To date, subjects who are smokers, have lung diseases etc. have been carefully excluded from long-term clinical studies, thus one must be careful about the potential side effects that will take place once inhaled insulin will be on the market and such patients use it over prolonged periods of time.

It is assumed that after inhalation many of the individual particles containing insulin are deposited at the lining of the smaller airways and alveoli. Potentially the high local concentration of insulin can stimulate (via a cross-reaction with IGF-1 receptors) proliferation of local cells or act as a tumour promoter. This is of particular concern in subjects exposed to carcinogens such as tobacco smoke. The (limited) amount of data available (from *in vitro* and *in vivo* preclinical animal experiments!) are reassuring. However, in view of the potential long-term exposure of patients with diabetes this is a topic which requires careful evaluation.

## When will inhaled insulin become available?

The side effects observed in phase III trials have delayed development (= apply for marketing approval) by several years, because the safety concerns necessitated additional long-term safety trials. Recently (March 04, 2004) Aventis and Pfizer announced that the European authorities (EMEA) accepted filing of a marketing authorisation application for Exubera. One has to see how the EMEA respond. Even if Exubera is approved in Europe, the question is whether the appropriate authorities in the US come to the same conclusion?

The next question is, will the healthcare provider reimburse this form of insulin therapy? If the metabolic effect achievable is comparable with that of sc insulin therapy, it is mainly the convenience argument which favours inhaled insulin. As discussed above, this can be an argument for specific groups of patients; however, healthcare providers might be reluctant to pay for this form of treatment. The development of inhaled insulin is a huge investment even for large pharmaceutical companies, but the expectations about the sales of Exubera vary considerably. Some expect it to be a blockbuster, and others assume that physicians will be very reluctant to prescribe it due to safety concerns. Even if Exubera is the front-runner now, probably in the long-run, arguments like a smaller device or a higher bioavailability (= lower price) might put other approaches in a position to takeover Exubera.

**Key messages**

- Inhaled insulin is rapidly absorbed
- Particle size is crucial
- Inhaled insulin provides a prandial metabolic control comparable to sc regular insulin
- Further optimisation is possible

## Conclusions

Due to the considerable progress made in the development of a pulmonary insulin application it can be predicted that very likely the pre-prandial inhalation of insulin will become the first practically applicable alternative to sc injections in the near future. The clinical-experimental studies show that the pharmacodynamic effects of inhaled insulin are at least as good as those with sc injection of regular insulin, with some devices even better than those observed with sc administration of rapid-acting insulin analogues. The clinical trials indicate that inhalation of insulin might prove especially beneficial for prandial insulin substitution in those patients with type 2 diabetes, who are reluctant to take injections and therefore continue to use oral agents, even if insulin therapy is indicated.

Most of the developments for inhaled insulin are focused on prandial insulin supply. Therefore it remains likely, that many patients still have to apply the long-acting insulin by means of one or two injections per day to cover basal insulin requirements. Clearly, replacement of this injection by inhalation would be favoured by patients. However, practically no progress has been made with respective developments.

If inhaled insulin becomes available for patients with diabetes and is a market success, it will most probably be a door opener for other peptides to be applied via this route of administration. Even today co-operation exist that aim to develop other peptides for treating diabetes (e.g. between MannKind and Novo Nordisk for GLP-I analogues) that can be applied via the lung.

The critical questions regarding the long-term consequences of the inhalation of insulin, i.e. the development of insulin-antibodies, changes in lung-function and lung safety which were raised during the clinical development appear to be answered by

appropriate long-term studies. However, detailed presentation of the results of these studies is lacking.

Cost-benefit issues must also be considered, particularly in light of the growing financial burden of type 2 diabetes for the healthcare systems. The premium costs of any new therapeutic option must be considered in the context of the potential optimisation of metabolic control, avoidance of hypoglycaemic events and the prevention of long-term complications. Appropriate studies investigating these aspects are missing. Should the pulmonary administration of insulin become available, diabetes would be the first systemic disease treated by this route of administration.

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