

# Inhaled insulin – the breakthrough in the treatment of diabetes?

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**Abstract:** Diabetes as a global epidemic is the fourth cause of death in the world currently. Ninety percent of all cases of diabetes represent patients with type 2 diabetes, in whom worsening of glycemic control is observed with progression of the disease. A number of trials which have been conducted so far showed that lack of sufficient glycemic control in both type 1 and type 2 diabetic patients accelerates progression of late complications of the disease. Although targets how to treat diabetes have been clearly defined few patients achieve them and maintain optimal metabolic control. Administration of insulin in type 1 diabetes is crucial for survival of the patients. Because of progressive course of the disease insulin is not rarely the only tool to achieve full normalization of glycaemia in type 2 diabetic patients. Chronic hyperglycemia in type 2 diabetic patients is the main reason to start insulin therapy. Decision about insulin administration is usually associated with patient's confusion and fear, mainly because of multiple subcutaneous injections and risk of hypoglycaemia or secondary weight gain. Studies on inhaled insulin have been successfully completed recently. In the spring of 2005 Exubera, the first insulin inhaler, was registered. The aim of this overview is to present the current clinical data on Exubera in the treatment of patients with type 1 and 2 diabetes.

**Key words:** inhaled insulin, type 1 diabetes, type 2 diabetes

Although symptoms of diabetes have been known for over 3.5 thousand years, it was however only in the last century that the correct understanding of the nature of this disease and the introduction of effective treatment methods took place. In several developing countries diabetes has reached the scale of an epidemic, at the same time being the fourth cause of death. [1]. Nearly 90% of diabetics are patients with type 2 diabetes [2]. In this disease, a gradual worsening of metabolic balance is observed with the disease progression, which requires the initiation of insulin administration [3]. Although it has been demonstrated that lack of sufficient glycemia control accelerates the development of late complications [4,5], an optimal metabolic balance (glycated hemoglobin [HbA<sub>1c</sub>] ≤7%) [6] is currently found only in 26% of type 2 diabetic patients in Poland, which results in the need of an earlier initiation of insulin therapy. Despite the fact that insulin is the best way of obtaining an efficient glycemia control, the decision about its initiation raises many fears among patients, especially because of the need of performing numerous injections [7].

Studies on inhaled insulin have been recently successfully completed. In the spring of 2007, Exubera, the first inhaler allowing the administration of inhaled insulin, was approved [8,9]. The aim of the present study is to present the currently available lines of clinical evidence, which can be helpful in the assessment of significance of this new drug in diabetes treatment.

## The respiratory tract as the route of drug administration

Several alternative ways of administration of insulin have been studied up to now, namely, transcutaneous nasal, oral and respiratory. The latter, for the presence of a large absorption area (about 145 m<sup>2</sup>), a thin and permeable alveolar membrane short of peptidases and an efficient perfusion, seems to be the most promising method of drug administration. The idea of using lungs as an insulin administration route appeared for the first time already in 1924 [10]. Gänslen, using insulin inhalation in a nebulizer, demonstrated a glycemia decrease in all the individuals studied [11]. However, this method has been found to be impractical in the treatment of diabetic patients because of differences observed in the bioavailability and variability with time. Studies performed in the 1980s and the 1990s have demonstrated that an effective drug supply to the alveoli also depends on the administered preparation molecule size, and 1–3 μm diameter molecules were considered to be

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**Table 1. Advantages of Exubera inhaled insulin administration [38]**

painless administration
large absorption surface – 140 m <sup>2</sup>
extensive vascular perfusion
thin alveolar-capillary membrane enabling a quick absorption of insulin molecules
rapid distribution to blood circulation (peak activity in 2 h)
drug action profile similar to physiologic insulin secretion in response to glycemia

optimal [12]. Apart from the size, also the form of the administered drug is of great significance. Therapeutic preparations inhaled as dry powder are characterized by a greater stability at room temperature, by lower sensitivity to microbiological factors and by the possibility of administering higher drug doses during one inhalation. The marketing of Exubera, a system that allows to deliver human insulin to the lungs in the form of dry powder packed in blisters, was a result of many years of studies.

### Pharmacokinetic properties of inhaled insulin

In the studies performed to date it has been demonstrated that inhaled insulin, as other rapid acting insulin analogues, is characterized by a more rapid onset of hypoglycemic action in comparison with human insulin administered subcutaneously [13,14]. Because of its speed of action (the onset already after 10–20 minutes from inhalation, peak at 2 h), the action profile of inhaled insulin resembles the physiological action profile of endogenous insulin (Tab. 1). The relative bioavailability of inhaled insulin in comparison with rapid-acting human insulin is about 6–10%. The application of a ten times higher dose of the drug is therefore necessary for glycemic normalization (Tab. 2).

In the study comparing the pharmacokinetics and pharmacodynamics of inhaled insulin, short acting human insulin and lispro insulin (both administered subcutaneously), a more rapid onset of action of inhaled insulin versus lispro and short acting insulin (respectively, 32, 41 and 48 min,  $p < 0.001$ ) has been demonstrated as well as a longer action time of inhaled insulin versus lispro insulin (387 vs. 313 min), and action time comparable with that of short acting insulin (387 vs. 415 min) [15]. The demonstrated time differences do not seem to be clinically significant. They indicate that inhalations of insulin may replace pre-prandial short acting insulin or rapid acting analogues injections.

### Inhaled insulin in type 1 diabetes treatment

Studies on type 1 diabetic patients confirm the efficacy and a good tolerance of inhaled insulin. Quattrin et al. [16] in the study including 335 patients with type 1 diabetes compared the efficacy of the two treatment models; pre-prandial inhaled

insulin and long acting insulin administered before sleep with a model of intensive insulin therapy (pre-prandial short acting insulin in combination with long acting insulin administered before sleep). In both groups a comparable decrease in HbA<sub>1c</sub> levels was observed (in the inhaled insulin treatment group from 8.1 to 7.9%, and in the human insulin treatment group from 8.1 to 7.7%). Although, taking into account the pharmacokinetic profile of inhaled insulin, a periprandial glycemia control was to be mainly expected, in the inhaled insulin group not only a greater postprandial glycemia reduction, but also fasting glucose reduction was observed. The inhaled insulin efficacy in glycemia control in patients with type 1 diabetes has also been confirmed by other authors [17]. However, despite promising findings regarding the safety of inhaled insulin and, what is most important, indicating the possibility of noninvasive insulin administration, so far, this type of therapy has not been registered for the use in patients <18 years of age, as current studies have been performed on adults.

### Inhaled insulin in type 2 diabetes treatment

Similar results concerning the efficacy of inhaled insulin in type 2 diabetic patients have been observed. In one of the studies 145 patients insufficiently balanced metabolically with the use of behavioral methods (diet, physical exercise) were randomized to inhaled insulin or to rosiglitazone [18]. Despite the fact that comparable initial HbA<sub>1c</sub> levels were observed in both groups (9.5 vs. 9.4%), a greater number of the inhaled insulin patients reached HbA<sub>1c</sub> levels of <8%. In three months inhaled insulin treatment resulted in a decrease in HbA<sub>1c</sub> levels of 7.2% in comparison with 8.0% observed in the rosiglitazone group. In another study 470 patients insufficiently treated with metformin alone were randomized according to HbA<sub>1c</sub> levels to either the inhaled insulin, or to the glibenclamide (glyburide) group for 6 months [19]. In the inhaled insulin group with the highest initial HbA<sub>1c</sub> level (>9.5%) a better glycemia control improvement and a greater treatment satisfaction level in comparison to the glibenclamide group have been demonstrated. The study by Testa et al. [20], assessing the inhaled insulin vs. metformin treatment, has been performed on 423 patients with type 2 diabetes treated to date with a sulfonylurea derivat. During a six-month follow up, in patients on inhaled insulin the mean HbA<sub>1c</sub> level decreased from 9.7% to 7.6%, and in metformin patients to 7.8% ( $p = 0.025$ ). What is more, the interruption of treatment was significantly more rarely observed in the inhaled insulin patients group (6% vs. 11%,  $p = 0.04$ ). A marked improvement in glycemia control concerned especially patients with the highest initial HbA<sub>1c</sub> level (>9.5%). In another study 299 patients, a six-month inhaled insulin therapy was associated with a better glycemia control, lower hypoglycemia occurrence, and, also, with a greater satisfaction level resulting from therapy as compared to the subcutaneous insulin group [21].

An important problem with patients diagnosed with type 2 diabetes represents a secondary inefficiency of oral hypoglycemics imposing the administration of insulin. A number

of short-term studies have demonstrated that the addition of inhaled insulin to oral therapy leads to an improvement in glycemia control. After 3 months of therapy with inhaled insulin in comparison to oral drugs, in 32% of patients a glycated hemoglobin level of  $>7.0\%$  has been achieved. In the group remaining exclusively on oral therapy only in 1% of the studied patients the target HbA<sub>1c</sub> values have been obtained [22]. Weiss et al. [23] have studied the effect of inhaled insulin in 68 type 2 diabetic patients who did not reach an adequate glycemia control with sulfonylurea derivate or metformin (initial HbA<sub>1c</sub> levels between 8.1–11.9%). Patients were randomized to the inhaled insulin or to the previous treatment method group. After 12 weeks of follow-up, an HbA<sub>1c</sub> reduction as well as a fasting glucose and postprandial glycemia decrease have been demonstrated only in the inhaled insulin group.

### Satisfaction with the treatment

The patient's sense of self-influence on the course of the disease plays an important role in the diabetes treatment process, because it is associated with the choice of treatment methods and with the fulfillment of doctors' indications [24]. In one of the studies, 779 patient who failed to obtain glycemia control with oral hypoglycemic drugs were randomized to either the group informed of the benefits and risks of subcutaneous insulin, or to the group informed of the benefits and risks associated with inhaled insulin [25]. Patients in the second group agreed to inhaled insulin therapy 3 times more often, which suggests that this option of treatment would allow for a more rapid intervention regarding glycemia control in chronically imbalanced patients who refuse to traditional insulin therapy. Completed studies demonstrated patients' greater satisfaction with inhaled insulin therapy [17,25,26]. During the 12-week follow-up of patients with type 2 diabetes a higher level of treatment satisfaction was observed in the inhaled insulin patient group than in the group of patients treated with insulin mixtures [26]. A higher level of treatment satisfaction correlated with a significant improvement in glycemia control expressed by HbA<sub>1c</sub> levels. In the Testa et al. study [20] it has been demonstrated that, despite more frequent side effects related to inhaled insulin (hypoglycemia, body mass gain), patients gained greater satisfaction with inhaled insulin treatment in comparison to metformin. In the three-month study by Gerber et al. [17] who evaluated the inhaled insulin treatment satisfaction in type 1 diabetic patients, glycemia control improvement was significantly better in the inhaled insulin treatment group (35.1% vs. 10.6%,  $p < 0.01$ ), and a decrease by 1% in HbA<sub>1c</sub> was associated with an 9.7% improvement in the treatment satisfaction.

### Side effects

In the frequently cited UKPDS study [27] it has been demonstrated that with the type 2 diabetes duration time the metabolic balance worsens, irrespectively of the type of hypoglycemic treatment used. All studies with the use of inhaled insulin, performed to date, assessed its efficacy in a short du-

**Table 2. Shortcomings associated to Exubera inhaled insulin administration**

providing glycemia control only periprandially
relative bioavailability of Exubera preparation compared to rapid acting human insulin is about 6–10%
most common undesirable symptom: cough

ration treatment. Its efficacy in the long term treatment, to which all diabetic patients are condemned, remains, therefore, unknown. Although insulin therapy can lead to a rise in the number of anti insulin antibodies, a higher titer of anti insulin antibodies has been observed in patients treated with inhaled insulin than in patients on human subcutaneous insulin [16]. It has been reported however that a higher titer of anti insulin antibodies does not incur changes in the HbA<sub>1c</sub> level, postprandial glycemia, insulin demand or the hypoglycemia incidents frequency [28,29]. In phase II and phase III studies of inhaled insulin administration the antibody titer stabilization was demonstrated after 12 months of therapy [30]. All performed to date studies of the inhaled insulin administration safety have lasted for several years, the humoral and cellular reactions after several years of inhaled insulin administration remain therefore unknown. Although, as suggested, the formation of anti insulin antibodies is commonly seen as insulin resistance, in view of current studies it seems that circulating immunological antibodies complexes may release insulin in a delayed time, which can lead to hypoglycemia and, in turn, complicate the insulin dosage. The risk of hypoglycemia during inhaled insulin treatment seems to be similar to or lower than the risk observed during subcutaneous insulin treatment, although all insulin preparations, with which inhaled insulin has been compared, show a different activity profile. In studies on type 2 diabetes, in which inhaled insulin treatment allowed for a significant HbA<sub>1c</sub> level reduction, the occurrence of hypoglycemia was more frequent than expected [22]. However, in the one-year follow up hypoglycemia frequency in individuals using oral hypoglycemic drugs (glibenklamide, metformin) or inhaled insulin was comparable in both groups [31]. Results of other studies do not seem to confirm the above finding, as in the three-month study comparing inhaled insulin treatment with rosiglitazone hypoglycemia episodes frequency was greater in the insulin treated group (0.7 vs. 0.0 incidents/person months), though none of the noted hypoglycemia episodes required the help of other people [32]. Also, in the study performed on patients with type 2 diabetes, which compared inhaled insulin administration applied together with ultra-long-acting insulin, and protamine insulin administration applied together with short acting insulin; a comparable decrease in HbA<sub>1c</sub> levels in both groups (8.1–7.9% vs. 8.1–7.7%), but a significantly lower frequency of hypoglycemia incidents in the inhaled insulin group (8.6 vs. 9.0 incidents/person months) have been demonstrated [16].

In all type 1 and type 2 diabetic patient studies performed to date, the adverse effect associated with inhaled insulin was

**Table 3. Side effects demonstrated in studies with the administration of Exubera inhaled insulin**

upper respiratory tract infections (sinuses, larynx, nose)
asthenia
headache, vertigos
nervousness, hyperhidrosis
cough (more frequent)
muscle trembling
hypoglycemia

cough (Tab. 3) [21,16], which went away or decreased during follow up. The presence of cough was not associated with lung function impairment assessed by: forced expiratory volume in the 1st second – FEV<sub>1</sub>, forced vital capacity – FVC or total vital capacity. There have been, however, reports on a significantly higher decrease in diffusing capacity for carbon monoxide during inhaled insulin treatment [16].

In inhaled insulin treatment studies, contrary to groups treated with subcutaneous insulin, body mass gain was not observed [21], although in all studies performed to date, administered doses of inhaled insulin were so small that they did not have to lead to secondary hyperinsulinemia syndrome.

### Specific situations

Some factors, as cigarette smoking, acute and chronic respiratory tract diseases and other inhalation drugs administration, may alter the pharmacokinetic and pharmacodynamic properties of the drug. In volunteers, who have been given inhalation insulin, pharmacokinetic differences of the preparation during respiratory tract infection and upon recovery were not found [33]. Lung function after inhalation insulin was assessed in another study including asthma patients. Comparing to the control group of healthy volunteers, in asthma patients clinically significant alterations in FEV<sub>1</sub> and FVC, or inhaled insulin induced bronchi hyperactivity episodes, were not demonstrated [34]. Despite the lack of differences regarding the time of maximal inhaled insulin action between both groups, a much lower insulin absorption and a greater maximal drug concentration in relation to the control group was demonstrated in asthma patients, suggesting that this type of hypoglycemic therapy may be an alternative only in patients with no coexisting chronic respiratory tract diseases. The simultaneous administration of bronchodilators may enhance the absorption of inhaled insulin and thus increase the hypoglycemia risk. Active cigarette smoking also significantly enhances the rapidity of absorption and the amount of inhaled insulin, being a contraindication to inhaled insulin administration. In the performed studies the concentration of drug found in smokers was three times higher than in nonsmokers [35]. Slight, but fixed differences regarding FEV<sub>1</sub> measurements in favor of the therapeutic group of inhaled insulin were demonstrated in clinical studies. In the study comparing inhaled insulin therapy

with oral hypoglycemics, an insignificant decrease in FEV<sub>1</sub>, which returned to normal in 12 weeks after the completion of the two-year therapy, was demonstrated in the group treated with insulin [36]. This indicates the necessity of lung sufficiency parameters assessment not only prior to the initiation, but also during the inhaled insulin therapy, although the currently available 4-year follow-up does not reveal fixed alterations in lung functional parameters.

### SUMMARY

In conclusion, the ongoing studies assessing the long-term safety, as well as other completed studies, show that inhaled insulin may become an efficient, accepted by patients tool in diabetes treatment [37]. Studies including type 1 or 2 diabetic adult patients have demonstrated that the efficacy of the Exubera preparation in obtaining glycemia control is equal to subcutaneous insulin. It has also been demonstrated that this drug contributes to a better glycemia control in type 2 diabetes patients who failed to obtain the metabolic balance with oral drugs. In addition, a greater level of treatment acceptance and satisfaction was demonstrated in inhaled insulin patients than in subcutaneous or oral insulin patients. As inhaled insulin is a drug that is just being introduced to the common treatment for diabetes, there is a need for further long-term clinical studies assessing the adequacy of insulin therapy and potential adverse effects associated with its long-term administration.

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