

Delivering Needle-Free Insulin Using AERx[®] iDMS (Insulin Diabetes Management System) Technology

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ABSTRACT

Background and Methods: Inhaled insulin has recently emerged as an alternative to subcutaneous insulin administration. One inhaled insulin device, AERx[®] (a registered trademark of Aradigm Corp., Hayward, CA, or its affiliates in the United States and other countries) insulin diabetes management system (iDMS) (Novo Nordisk A/S, Bagsværd, Denmark), uses a unique liquid human insulin strip to deliver an aerosol of insulin to the lungs. AERx iDMS enables 1-unit increment dosing, and the device ensures that the insulin dose is released at the optimal point of inhalation for delivery to the lungs.

Results: Compared with subcutaneous human insulin, the pharmacokinetic and pharmacodynamic profile of inhaled insulin with AERx iDMS is similar, but with a more rapid onset of action. Data from these pharmacokinetic studies have also demonstrated that inhaled insulin dosing with AERx iDMS is as consistent and reproducible as subcutaneous human insulin.

Conclusions: In individuals with diabetes, prandial inhaled insulin with AERx iDMS is as effective and well tolerated as subcutaneous prandial human insulin or insulin aspart in terms of glycemic control and overall hypoglycemia. No major safety concerns have been raised with respect to pulmonary function tests. Other clinical studies using AERx iDMS in special populations, such as smokers, people with asthma, or people suffering from upper respiratory tract infections, have provided important information regarding the use of inhaled insulin in these circumstances. Overall, pulmonary insulin delivery with the AERx iDMS device appears to be a promising safe and efficacious alternative to subcutaneous insulin injections.

INTRODUCTION

INSULIN IS THE CURRENT standard treatment for people with type 1 diabetes, and emerging evidence suggests the same for people with type 2 diabetes. Data from the Diabetes Control and Complications Trial¹ and its follow-up trial Epidemiology of Diabetes Interventions

and Complications² in type 1 diabetes, as well as the United Kingdom Prospective Diabetes Study³ and the Kumamoto study in type 2 diabetes,⁴ have all demonstrated the benefits of achieving tight glycemic control with insulin regimens.

Ever since its discovery in the 1920s, the primary route of insulin administration has been

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subcutaneous (s.c.) injection. With intensive insulin regimens, individuals with diabetes may inject themselves four or more times a day.

There is a need to explore other routes of insulin administration for those people who do not want to or cannot administer multiple s.c. insulin injections. Many alternative routes of administration have been investigated over the years,⁵ but it is the inhaled insulin devices that currently appear to have the most potential, with several devices in clinical phase III trials and one now approved for use in the United States and Europe.

This review will cover the technological and clinical data available with respect to inhaled insulin administered via AERx[®] (a registered trademark of Aradigm Corp., Hayward, CA, or its affiliates in the United States and other countries) insulin diabetes management system (iDMS) (Novo Nordisk A/S, Bagsværd, Denmark).

TECHNOLOGICAL REQUIREMENTS FOR INHALED INSULIN DEVICES

The lungs have a large surface area (approximately 100 m² in adults) and are covered with a thin alveolar epithelium (0.1–0.5 μ m); this allows for rapid absorption of inhaled drugs into the circulation.⁶ The lungs therefore offer a potential route for insulin administration. Deposition of inhaled insulin in the deep lung is optimal, and certain parameters have to be controlled in order to achieve successful systemic absorption: only aerosolized particles with a mass median diameter of less than 5 μ m are deposited in and absorbed through the alveoli, with the ideal particle size less than 3 μ m in diameter.⁶ Larger particles (>6 μ m) tend to be deposited in the oropharynx, and particles less than 1 μ m are exhaled during normal breathing.⁶ Other parameters include the patient's breathing technique: low inhalation flow rate promotes particle deposition in the lung periphery. Aerosol delivery should preferably be automatically synchronized with the patient's inhalation. These factors, among others, can contribute to the bioavailability of inhaled insulin.

Accurate and reproducible dosing is essential for individuals with diabetes, as optimal treatment requires tight blood glucose control obtained through frequent dose adjustments. A

device that delivers insulin via inhalation has to ensure that dosing is precise in order to avoid unnecessary hyper- or hypoglycemia, and also to ensure patient and physician confidence in the treatment.

AERx iDMS

AERx iDMS is a system for pulmonary delivery of insulin. It consists of a device that incorporates an electronic system that helps to guide users' breathing and an insulin strip that delivers liquid human insulin aerosol droplets to the deep lung. The disposable, single-use, sterile insulin strip contains liquid insulin within a blister on the strip. Upon activation, the insulin is extruded through hundreds of 1- μ m-diameter laser-drilled holes, producing an aerosol spray of fine particles 2–3 μ m in diameter, therefore maximizing the amount of insulin that reaches the deep lung.⁷ The insulin strip can deliver the approximate equivalent of 2–10 IU doses per strip, and allows for 1-unit increment dosing. AERx iDMS also ensures, via breath control activation, that the insulin is only released when the inspiratory flow rate of the inhaling patient is optimal for deep lung delivery. The device has a patient guidance system that aims to minimize errors and ensure that only the dialed dose of insulin is being released from the device. An early study showed successful drug deposition using gamma scintigraphic imaging.⁸ The study reported a 53.3% lung deposition with the inhaled technology administration compared with 21.1% deposition with a traditional metered dose inhaler device used for respiratory diseases.⁸

Some of the unique characteristics of AERx iDMS include the liquid insulin formulation and that insulin can be dosed in 1-unit increments (Table 1).^{9–11}

CLINICAL EXPERIENCE WITH AERx iDMS

Pharmacodynamic and pharmacokinetic profile of insulin delivered with AERx iDMS

The pharmacokinetic and pharmacodynamic profile of inhaled human insulin via AERx iDMS (with doses of 0.3, 0.6, 1.2 and 1.8 U/kg)

TABLE 1. CHARACTERISTICS FOR AERx iDMS AND OTHER INHALED INSULIN DEVICES

<i>Device</i>	<i>Insulin formulation</i>	<i>Dosing</i>	<i>Dose linearity</i>
AERx iDMS	Liquid insulin	1-unit increments	Yes
Exubera® (Barnett, 2004) ⁹	Dry powder insulin	1- and 3-mg increments	No
AIR (Rave et al., 2005) ¹⁰	Dry powder insulin	2- and 6-unit increments	Yes
Technosphere (Pfützner and Forst, 2005) ¹¹	Insulin plus drug carrier	Unknown	Unknown

has been compared with that of s.c. injected human insulin (0.12 IU/kg) in a randomized, open-label, five-period crossover euglycemic clamp study of 18 individuals with type 1 diabetes.¹² Inhaled insulin using AERx iDMS demonstrated a clear dose–response relationship. The mean time to maximum insulin concentration for 1.2 U/kg was 62 min for inhaled human insulin via AERx iDMS compared with 119 min for the equipotent s.c. human insulin dose). The pharmacodynamic profile reflected the pharmacokinetic results: the time to maximum glucose infusion rate for AERx iDMS was 157 min compared with 189 min for s.c. insulin. Thus, the pharmacokinetic and pharmacodynamic profiles indicated that inhaled insulin produces a more rapid onset of action than s.c. human insulin.¹² Another similar study has confirmed dose linearity for pharmacokinetic and pharmacodynamic parameters of inhaled insulin with AERx iDMS. This study likewise demonstrated shorter mean time to maximum insulin concentration for inhaled insulin using the AERx iDMS compared with s.c. human insulin.¹³

As the pharmacokinetic and pharmacodynamic profiles of inhaled human insulin mimic those seen with the rapid-acting insulin analog, insulin aspart, in the onset of action, it appears that inhaled insulin is suitable for prandial administration.¹⁴ Data show that the duration of insulin action with AERx iDMS is similar to that of s.c. human insulin—approximately 300 min, as defined by 10–90% of the area under the curve (AUC) for the glucose infusion rate from 0 to 10 h.¹⁴

A reproducible response to identical doses of insulin is imperative in the quest for tight glycemic control; periods of hyperglycemia and/or hypoglycemia can have serious and long-lasting adverse effects for people with diabetes. Consequently, day-to-day variation in

insulin response needs to be kept at a minimum where possible. Intrasubject variability has been measured (via serum glucose and serum insulin measurements every 6 h) with AERx iDMS in 17 individuals with type 1 diabetes who were given s.c. human insulin or inhaled human insulin with AERx iDMS on four consecutive days.¹⁵ There was no statistically significant difference between the two administration routes with regards to intrasubject coefficients of variation for different pharmacokinetic/pharmacodynamic end points, including the main end-point percentage coefficients of variation of AUC for insulin from 0 to 6 h ($AUC_{ins0-6\text{ h}}$): 27% versus 19% ($P = 0.15$).¹⁵ These data suggest that dosing with AERx iDMS is as reproducible and consistent as dosing with s.c. human insulin.

Long-term efficacy and safety with AERx iDMS

The efficacy and safety of the AERx iDMS system have been investigated in a randomized, open-label, multinational, parallel-group, clinical proof-of-concept trial.¹⁶ In this trial, 107 people with type 2 diabetes were randomized to receive prandial inhaled human insulin via AERx iDMS or s.c. human insulin, both three times daily and both with bedtime s.c. NPH insulin, for 12 weeks. Insulin doses were based on the individual's previous dose. Dose was titrated according to blood glucose targets (fasting blood glucose ≤ 5.5 mM; postprandial blood glucose < 7.5 mM); single-unit dosing with AERx iDMS enabled easy titration. A decrease in hemoglobin A_{1c} (HbA_{1c}) in both groups was observed during the study, and there was no statistically significant difference in mean HbA_{1c} between the inhaled insulin group and the s.c. insulin group at study end ($7.84 \pm 0.77\%$ vs. $7.76 \pm 0.77\%$, $P = 0.60$) (Fig. 1). Interestingly, mean fasting serum glucose

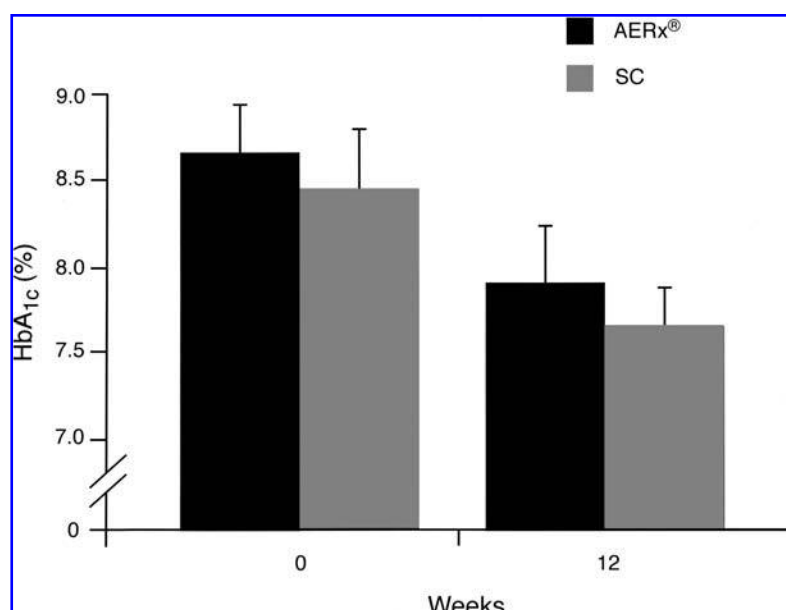


FIG. 1. Mean HbA_{1c} before and after 12 weeks of treatment with AERx iDMS and s.c. insulin.¹⁶ Black bars represent AERx iDMS, and gray bars represent s.c. insulin. Reprinted with permission from the American Diabetes Association.

was lower in the inhaled insulin group than in the s.c. insulin group after 12 weeks of treatment: 8.9 ± 3.8 vs. 10.8 ± 4.7 mM ($P = 0.01$). The percentage coefficient of variation of fasting blood glucose was similar with both treatments: 30.3% for inhaled insulin versus 27.3% for s.c. insulin ($P = 0.34$). Inhaled insulin with AERx iDMS also resulted in similar prandial blood glucose increments as s.c. insulin (2.0 ± 2.1 vs. 1.3 ± 2.2 mM, $P = 0.12$). Overall, it appeared that inhaled insulin with AERx iDMS delivered glycemic control as good as that with s.c. insulin.

In this study, the overall rates of hypoglycemic events per month were similar between the two treatment groups (1.05 in the inhaled insulin group vs. 1.52 in the s.c. insulin group, relative risk 0.69, $P = 0.11$).¹⁶ Likewise, pulmonary function tests (forced vital capacity, forced expiratory volume in 1 s, forced expiratory volume in 1 s as a percentage of forced vital capacity, total lung capacity, and lung diffusing capacity for carbon monoxide) showed no difference in change from baseline between the two groups.

A long-term, randomized, open-label, parallel-group safety study also compared pulmonary safety and glycemic control between preprandial inhaled human insulin via AERx iDMS and s.c. insulin aspart, both with once- or twice-daily s.c. NPH insulin, in people with type

1 diabetes.¹⁷ In this study conducted over 12 months in 299 individuals with type 1 diabetes, HbA_{1c} levels with inhaled insulin were noninferior to those of s.c. insulin aspart (7.74% vs. 7.56%, respectively, difference not significant).¹⁷ Fasting plasma glucose levels were again lower in the inhaled insulin group, compared with those in the s.c. insulin aspart group (9.17 mM vs. 11.7 mM, $P < 0.01$), but mean prandial glucose increment was higher in the inhaled insulin group (2.12 mM vs. 0.21 mM, $P < 0.01$). From baseline, mean body weight decreased 1.2 kg with inhaled insulin but increased 1.3 kg with s.c. insulin aspart ($P < 0.01$). Pulmonary function tests were similar between groups except for lung diffusing capacity for carbon monoxide, which was slightly decreased with inhaled insulin compared with s.c. insulin aspart (estimated percentage of predicted: 84.39% vs. 86.42%). The risk of overall hypoglycemia was similar with inhaled insulin and s.c. insulin.¹⁷

Other safety aspects of AERx iDMS and special populations

Inhaled insulin could pose certain risks with its use in special patient populations, such as smokers, people with asthma, or during a concurrent upper respiratory tract infection.

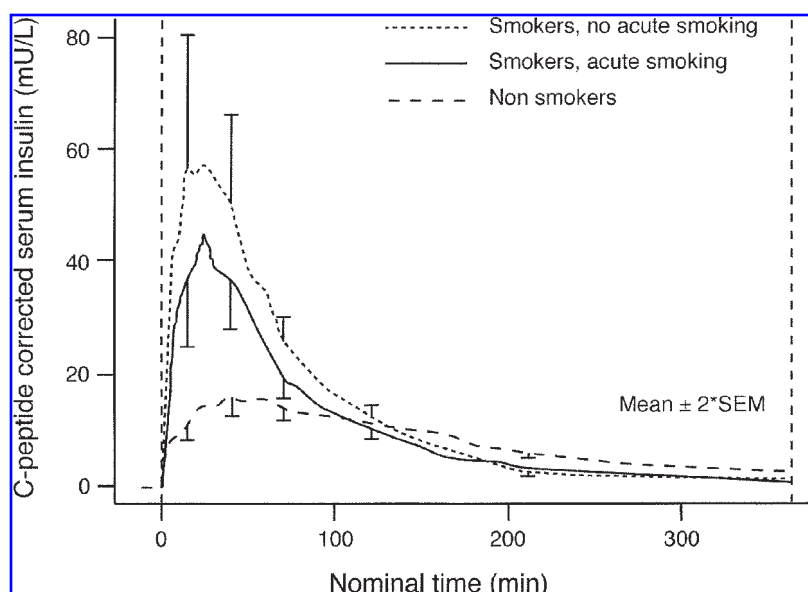
One of the first studies to address inhaled insulin in people without diabetes who smoke

was conducted with AERx iDMS in 27 smokers and 16 nonsmokers. In this randomized, two-period crossover trial, individuals received a single inhaled insulin dose via AERx iDMS on 2 days.¹⁸ On one dosing day, smokers indulged in “acute smoking” of three cigarettes immediately before insulin administration. On the other dosing day, “nonacute smoking” was achieved by abstaining from smoking from midnight. Serum insulin profiles showed statistically significant pharmacokinetic differences between the two groups: in comparison with the nonsmoking group, approximately 60% more insulin was absorbed in the smoking group ($AUC_{ins0-6\text{ h}}$: 63.2 mU/L/h vs. 40.0 mU/L/h, $P = 0.002$) (Fig. 2). Furthermore, the mean maximum insulin concentration was approximately three times higher in the smoking group (42.0 mU/L vs. 13.9 mU/L, $P < 0.0001$), and the time to maximum insulin concentration was statistically significantly faster in the smoking group (31.5 vs. 53.9 min, $P < 0.001$). Pharmacokinetic differences were also seen between acute and nonacute smoking: insulin absorption was reduced by 22% ($AUC_{ins0-6\text{ h}}$: 55.8 mU/L/h vs. 71.5 mU/L/h, $P < 0.001$), and likewise maximum insulin concentration was reduced by 23% (36.8 mU/L vs. 47.8 mU/L, $P = 0.001$) following acute smoking compared with nonacute smoking. The estimated intrasubject variability of $AUC_{ins0-6\text{ h}}$

was 13.7% and 16.5% for nonsmokers and smokers, respectively. These findings show that inhaled insulin with AERx iDMS is more variable in people who smoke and that acute or chronic smoking can alter insulin absorption further. The impact of these variations in inhaled insulin absorption in smokers will limit the safe and efficacious use of inhaled insulin in this population.

Inhaled insulin in people with untreated asthma was also studied using AERx iDMS, in comparison with a group without asthma: insulin absorption was lower in the people with untreated asthma compared with the healthy controls. Furthermore, no increase in airway hyper-responsiveness due to insulin inhalation was observed in the asthma group.¹⁹ A total of 28 controls without asthma and 17 individuals with untreated asthma inhaled single insulin doses (~ 6 IU of s.c. insulin) via AERx iDMS on two dosing days: serum insulin profiles showed that mean $AUC_{ins0-6\text{ h}}$ was statistically significantly lower in individuals with untreated asthma (1.07×10^6 vs. 1.45×10^6 pM $\cdot$ min $\cdot$ kg, $P = 0.013$). Correspondingly, the AUC for glucose from 0 to 6 h was also statistically significantly lower (3,419 mg/dL/min vs. 4,880 mg/dL/min, $P = 0.007$). In the second part of the study, after a higher dose was administered, pulmonary function tests were also assessed before and after dosing, and there

FIG. 2. Mean exogenous serum insulin concentrations with AERx iDMS in smokers and nonsmokers.¹⁸ Single black line represents smokers, acute smoking; unequal dashed black line represents smokers, no acute smoking; equal black dashed line represents nonsmokers. Reprinted with permission from the American Diabetes Association.



were no clinical symptoms, or any instance of increased airway hyper-responsiveness, in either group. From these results, it appears that people with diabetes and untreated asthma may absorb less inhaled insulin than people without asthma but with diabetes.¹⁹ Further investigations are needed to determine the effects of asthma treatments on inhaled insulin absorption.

Using AERx iDMS during a concomitant uncomplicated upper respiratory tract infection (common cold) has been investigated in a study of 20 individuals without diabetes suffering from an upper respiratory tract infection, who were given a single dose of insulin (~6 IU of s.c. insulin) via AERx iDMS. In symptomatic people studied during a viral infection, and then following spontaneous recovery, it was found that the pharmacokinetic and pharmacodynamic parameters of inhaled insulin were not altered.²⁰ Consequently, upper respiratory tract infection should not compromise inhaled insulin absorption.

Other long-term safety issues with inhaled insulin include the effect of insulin administration on lung cell proliferation and fibrosis. Preclinical 3-month and 9-month data with high doses of inhaled insulin in rats and monkeys have shown no treatment-related effects relevant for human safety (data on file, Novo Nordisk). In particular, no signs of increased proliferative cellular activity were found using proliferating cell nuclear antigen staining, no increased collagen using Masson's trichrome staining, or other treatment-related histological changes in the lung of either rats or monkeys (data on file, Novo Nordisk).

Another safety issue with inhaled insulin is the development of insulin antibodies. Any exogenous administration of insulin can evoke an immunological response, and, indeed, it has been shown that insulin antibodies may develop in up to 80% of people treated with s.c. human insulin.²¹ Consequently, it is very reasonable to assume that people receiving inhaled insulin would also develop insulin antibodies. Some studies have shown that insulin antibody levels increase with the use of inhaled insulin in comparison with s.c. insulin, although these changes were not related to any adverse clinical consequences.²² Insulin anti-

body levels were measured during the 12-week clinical proof-of-concept trial with AERx iDMS in people with type 2 diabetes previously treated with human insulin.¹⁶ Although 12 weeks might not be a sufficient duration in which to temporally measure insulin antibody levels, this study still provides interesting data, in addition to the longer-term data^{17,23} described below, regarding insulin antibody development with AERx.¹⁶ The median total insulin antibody level did increase from 6% to 35% trace binding of total antibodies in the inhaled insulin group, while there was no change in the s.c. insulin group.¹⁶ However, no correlation was found between the change in total insulin antibody level and metabolic control or insulin dose, and no clinical signs or symptoms were reported in relation to the change in the AERx iDMS group. Furthermore, the observed increases in antibody levels are similar to those reported with long-term use with s.c. insulin aspart.²⁴ Insulin antibody response was also measured in a long-term study comparing inhaled insulin via AERx iDMS with s.c. insulin aspart in people with type 1 diabetes: total and IgG insulin antibody levels were higher with inhaled insulin than insulin aspart.¹⁷ Further analyses in a subgroup of people treated for 23 months showed no evidence of an influence of elevated antibody levels on pharmacokinetic characteristics after a single inhalation of inhaled insulin or over three mealtime inhalations.²³

Compliance with AERx iDMS

High compliance with inhaled insulin using AERx iDMS was observed in the 12-week clinical proof-of-concept trial in 49 people with type 2 diabetes monitored for a mean of 78.9 days and 226 doses.²⁵ Using data recorded by the AERx iDMS system, the average compliance rate for the preprandial dosing regimen was 94.3% (SD 9.1; range 45–100) for the prescribed number of daily doses. Inhalation technique was also very good, with less than 2.5% of participants experiencing inadequate inhalation with one to five doses.²⁵

The weight of the current device may be perceived as inconvenient for patients, although there are no data to suggest this affects compliance.

CONCLUSIONS

In summary, AERx iDMS addresses and fulfills the parameters required for efficient deep lung drug delivery. Furthermore, inhaled insulin with the AERx iDMS device demonstrates similar efficacy as s.c. human insulin and insulin aspart in people with type 1 or type 2 diabetes. Inhaled insulin with AERx iDMS is well tolerated, and no major safety concerns have been raised. However, further studies with AERx iDMS are needed to establish the reversibility of insulin antibody formation and pulmonary function changes, as well as long-term effects on the lungs. Overall, pulmonary insulin delivery with the AERx iDMS device appears to be a promising safe and efficacious alternative to s.c. insulin injections.

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