Intensive Therapy With Inhaled Insulin via the AERx Insulin Diabetes Management System

A 12-week proof-of-concept trial in patients with type 2 diabetes

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OBJECTIVE — To compare the glycemic control of inhaled insulin via the AERx insulin diabetes management system (iDMS) with that of subcutaneous (SC) insulin, both combined with NPH insulin at bedtime, in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — The AERx iDMS uses a liquid insulin formulation to achieve flexible precise mealtime dosing (with increments corresponding to 1 IU administered subcutaneously) and ensures insulin delivery only when the breathing technique is optimal. This trial in patients with type 2 diabetes compared the glycemic control (HbA_{1c}) achieved by inhaled insulin administered via AERx iDMS with that using SC insulin. This was a randomized, 12-week, open-label, parallel, multicenter, multinational trial in 107 nonsmoking patients with type 2 diabetes (mean age 59 years, mean duration of diabetes 11.9 years). Patients were randomized to receive either inhaled fast-acting human insulin via AERx iDMS immediately before meals or SC fast-acting human insulin administered 30 min before meals, both in combination with evening NPH insulin.

RESULTS — Baseline and demographic characteristics were similar between the two groups. There was no statistically significant difference in HbA_{1c} between the AERx and SC groups after 12 weeks of treatment (7.84 ± 0.77 vs. 7.76 ± 0.77%, $P = 0.60$). Fasting serum glucose was significantly lower in the AERx group compared with the SC group by the end of the trial (8.9 ± 3.8 vs. 10.8 ± 3.7 mmol/l, $P = 0.01$) with a similar NPH dose in the two groups (0.23 vs. 0.23 IU/kg, $P = 0.93$). There were no statistically significant differences between the two groups in the intra-subject variability of fasting or prandial blood glucose increment. Adverse events were similar in the two groups. No major safety concerns were raised during the trial.

CONCLUSIONS — In patients with type 2 diabetes, preprandial inhaled insulin via AERx iDMS is as effective as preprandial SC insulin injection in achieving glycemic control with similar tolerability.

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Many patients with type 2 diabetes initially achieve adequate glycemic control with diet, exercise, and oral antidiabetic medication. However, most patients eventually require exogenous insulin injections to attain glycemic control targets (1). Despite this, patients and physicians appear to be hesitant to use insulin, and, consequently, patients remain in poor glycemic control (2–5). Needle anxiety is one of the factors associated with this reluctance (6,7); therefore, new routes of insulin administration could be used to achieve and maintain optimal glycemic control.

Presently, the alternatives to subcutaneous (SC) injections of insulin are limited. The only existing clinical alternative is continuous SC insulin infusion, or insulin administered by means of an implantable pump. This alternative is mainly recommended and used in patients with type 1 diabetes. One recent development is that of inhaled insulin systems, and current published data have shown the clinical viability of inhaled insulin in all patients with diabetes (8,9).

The AERx insulin diabetes management system (iDMS) addresses factors such as particle size (10) and breathing technique (11,12), which have to be correctly controlled if inhaled insulin is to be clinically feasible. AERx iDMS delivers, from a unique insulin strip, liquid insulin aerosol droplets (1–3 μm) to the deep lung, only during precise predefined inspiratory flow and volume (12). The device is designed to ensure insulin delivery only when the breathing technique is optimal (breath check); it also records insulin dose and patient use to allow physicians to track compliance and inhalation technique, thereby improving treatment outcome. Pharmacological studies have demonstrated that AERx iDMS produces a rapid onset of glucose-lowering activity, with a clear dose response (13). Furthermore, in all the preclinical and human pharmacology

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Abbreviations: FBG, fasting blood glucose; FSG, fasting serum glucose; iDMS, insulin diabetes management system; PFT, pulmonary function test; SC, subcutaneous; TEAE, treatment emergent adverse event.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

studies performed so far, inhaled insulin via AERx iDMS has been well tolerated, with no adverse effects on pulmonary function tests, and has not caused any safety concerns. For this new system to become a feasible treatment tool for diabetes, it needs to be similar to SC insulin in terms of efficacy and safety.

The primary objective of this clinical proof-of-concept trial in patients with type 2 diabetes was to compare the glycemic control of inhaled insulin via the AERx iDMS with that of SC insulin, both combined with NPH insulin at bedtime.

RESEARCH DESIGN AND METHODS

— The trial was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committees. All participants gave informed written consent before starting the trial.

Study population

This study was a randomized, open-label, parallel, multicenter, multinational trial in 107 patients with type 2 diabetes. All participants had been diagnosed with diabetes and had been treated with insulin (any insulin regimen, but not treated with an oral antidiabetic drug) for >6 months. To be included in the trial, patients had to be nonsmokers between the age of 30 and 75 years, with a BMI of ≤35.0 kg/m^2 and with HbA_{1c} levels ≥6.6 and ≤11.0%. All patients had to be deemed competent to undertake an intensive insulin regimen. All participants had to possess acceptable pulmonary function as defined by screening forced vital capacity and forced expiratory volume >70% of predicted normal values for age, sex, and height. Patients with any pulmonary disease were excluded.

Study protocol

The trial consisted of a screening visit (visit 1) and six trial visits (visits 2–7) during the treatment period of 12 weeks. After visit 1, patients were randomized to either of the following:

- Fast-acting human insulin administered via the AERx iDMS immediately before breakfast, lunch, and dinner, combined with SC NPH insulin (Insulatard) at bedtime (AERx group) *or*
- Fast-acting human insulin (Actrapid) administered subcutaneously 30 min before breakfast, lunch, and dinner, combined with SC NPH insulin (Insulatard) at bedtime (SC group).

Insulin doses were first based on the patients' previous insulin requirements. One AERx unit (1 unit in the device display) of inhaled insulin via the AERx iDMS was anticipated to correspond to the effect of ~1 IU of SC insulin. This calculation was based on previous pharmacokinetic and pharmacodynamic studies (13). The total amount by mass of insulin in 1 AERx unit is ~7.5 times higher than that in 1 IU human soluble insulin. The AERx dose could be adjusted with increments of 1 unit. A maximum dose of 30 AERx units could be used for each premeal dose, whereas no maximum dose was determined for SC insulin. Dose titration targets, as defined in the study protocol, were fasting blood glucose (FBG) ≤5.5 mmol/l and postprandial blood glucose <7.5 mmol/l.

In the event that the AERx iDMS could not be used, fast-acting human insulin (Actrapid) was to be administered subcutaneously as "escape therapy".

Efficacy end points

The primary efficacy end point was HbA_{1c} after 12 weeks of treatment. Secondary efficacy end points included laboratory-measured fasting serum glucose (FSG) and insulin doses after 12 weeks of treatment, plus a home-measured nine-point blood glucose profile and blood glucose measurements for variability before and after breakfast and lunch for 3 days, both performed in the last week of the treatment period. Blood samples were taken at visit 1 and visit 7 for measurement of HbA_{1c} and FSG. The bioeffectiveness of inhaled insulin relative to SC insulin was calculated as the ratio between mean doses that produced the same therapeutic effect (HbA_{1c}). The "emitted dose" was the dose (in units) actually delivered by the AERx iDMS and was calculated as follows: dose in AERx units/10 (number of strips) × 75 units per strip × 0.628, where 75 units is the insulin content in one insulin strip and 0.628 is a technical device parameter.

Safety

Safety end points were recorded at various points throughout the 12-week treatment, including standard pulmonary function tests (PFTs), insulin-specific antibodies (total and subclass IgA, IgG, and IgE), incidence of hypoglycemic episodes, type and incidence of adverse events, and laboratory and other parameters. Also recorded were the number and type of AERx iDMS problems, the time spent by the clinical staff (for instruction in the use of the trial device) at every contact with the patient, and the incidence of patient "sick leave" days. Contact was defined as contact with the patient where time spent discussing device issues was >0 min.

Statistical methods

The study was powered with a 95% CI (total width of 1% absolute) to detect treatment difference in HbA_{1c} after 12 weeks. A 5% significance level was used for all analyses. Analysis of HbA_{1c} and FSG was performed in the intention-to-treat population. An ANOVA model was used with baseline HbA_{1c} as a covariate, patient as a random effect, and treatment, center, and sex as fixed effects. Analyses of prandial blood glucose increment and FBG from the nine-point blood glucose profile and the intrasubject day-to-day variabilities of FBG and prandial blood glucose increment were performed using an ANOVA model in the per-protocol population only (all eligible randomized patients completing the trial according to

Table 1—*Patient characteristics*

	AERx	SC	Total
Subjects exposed (*n*)	54	53	107
Sex (*n*) (M/F)	32/22	35/18	67/40
Age (years)	59.5 ± 7.4	57.9 ± 9.7	58.7 ± 8.6
BMI (kg/m^2)	27.6 ± 3.4	27.8 ± 3.4	27.7 ± 3.4
Duration of diabetes (years)	10.7 ± 7.2	13.0 ± 7.8	11.9 ± 7.5
HbA_{1c} (%)	8.6 ± 0.9	8.5 ± 1.2	8.5 ± 1.1
Fasting serum glucose (mmol/l)	11.4 ± 4.1	11.7 ± 3.6	11.6 ± 3.9

Data are means ± SD unless otherwise indicated.

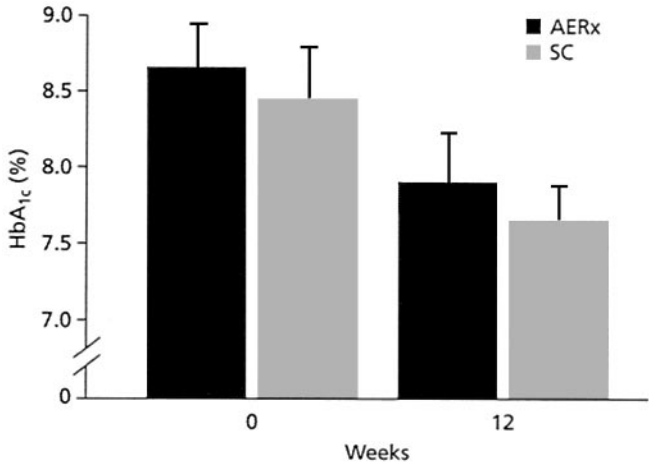

Figure 1—*Mean HbA_{1c} before and after 12 weeks of treatment (intention-to-treat population). There was no difference in the change in HbA_{1c} between the groups* (P = *0.60).*

protocol and using escape therapy in <20% of expected administrations). Daily insulin doses (basal and bolus) as well as safety end points were summarized by treatment. A post hoc calculation of the bioeffectiveness of AERx iDMS was also made. All values are given as means ± SD unless otherwise stated.

RESULTS

Patient demographic characteristics

The AERx and SC groups were similar in all respects (Table 1) and represented a typical Scandinavian population of patients with type 2 diabetes. In total, 109 patients were randomized, of whom 107 (54 AERx, 53 SC) were given at least one dose of the study drug. These individuals comprise the population for the intention-to-treat and safety analyses. There were 98 patients who completed the trial. A total of 11 patients withdrew (6 AERx vs. 5 SC). The reasons for withdrawal were adverse events (2 AERx), ineffective therapy (1 AERx), noncompliance (2 AERx vs. 3 SC), and other reasons (1 AERx vs. 2 SC). The per-protocol population included 96 patients (47 AERx vs. 49 SC). A total of 101 patients took two or more insulin injections per day in their prestudy insulin regimen.

Efficacy

There was no statistically significant difference in HbA_{1c} between the AERx and SC groups after 12 weeks of treatment (7.84 ± 0.77 vs. 7.76 ± 0.77%, P = 0.60). A decrease in HbA_{1c} was observed in both groups during the study (Fig. 1). There was no statistically significant difference in change from baseline in mean HbA_{1c} between the two groups after 12 weeks of treatment (−0.69 ± 0.77 vs. −0.77 ± 0.77%, P = 0.60).

FSG at baseline in the two groups was similar, but after 12 weeks of treatment, was significantly lower in the AERx group (8.9 ± 3.8 vs. 10.8 ± 3.7 mmol/l, P = 0.01).

There was no statistically significant difference in prandial blood glucose increment between the AERx and SC groups (2.0 ± 2.1 vs. 1.3 ± 2.2 mmol/l, respectively, P = 0.12). Intrasubject variability in the AERx group was as good as in the SC group (FBG % coefficient of variation [95% CI]: 30.3 [25.9–35.0] vs. 27.3% [23.8–32.1], P = 0.34; prandial blood glucose increment 27.1 [22.9–30.9] vs. 26.9% [23.4–31.7], P = 0.95). There was no statistically significant difference between the AERx group and the SC group in FBG levels based on the nine-point blood glucose profile (7.04 ± 2.0 vs. 7.78 ± 2.1, P = 0.08) or indeed the overall analysis of the blood glucose profile (P = 0.34). Approximately 40% of the measurements in each group (AERx 37%; SC 36%) achieved the postprandial blood glucose target of <7.5 mmol/l stated in the protocol.

After 12 weeks of treatment, the mean meal-related insulin dose in the AERx group (AERx units/kg) was higher than that in the SC group (IU/kg) (0.40 ± 0.41 vs. 0.34 ± 0.42, P = 0.03). The ratio between these mean meal-related insulin doses in the two groups was 0.85 IU SC insulin per AERx unit delivered by the device. The mean basal insulin dose in the AERx group was not statistically significantly different from that in the SC group after 12 weeks of treatment (both groups 0.23 IU/kg, P = 0.93). The bioeffectiveness of the AERx iDMS was calculated to be 17% on the basis of emitted dose.

Safety

The number of treatment emergent adverse events (TEAEs) and number of patients experiencing TEAEs were similar in the two treatment groups. In the AERx group, 29 (54%) patients experienced 52 TEAEs, whereas 29 (55%) patients reported 57 TEAEs in the SC group. The most frequent events were headache (5 AERx vs. 4 SC patients), upper respiratory tract infection (4 vs. 8), and diarrhea (3 vs. 2), and most TEAEs were mild or moderate.

Three major hypoglycemic episodes (an episode where the patient required third-party assistance) were reported by two patients in the AERx group. No major hypoglycemic episodes were reported in the SC group. In total, there were numerically fewer hypoglycemic events in the AERx group than in the SC group (151 vs. 211). However, the rate of events per month was 1.05 in the AERx group and 1.52 in the SC group. The relative risk of hypoglycemia with AERx/SC was 0.69 (P = 0.11).

Mean values of PFTs are given in Table 2. There were no significant differences between the two groups for any of the PFTs in change from baseline (Table 2). On an individual basis, both increases and decreases in pulmonary function were observed and distributed equally within and between the two groups. However, only decreases in the AERx group were recorded as adverse events and followed up, even though the same changes were seen in the SC group.

Follow-up PFTs after the trial by a pulmonary specialist with the two patients in the AERx group who experienced a decrease in pulmonary function showed that lung functions had returned toward baseline values. No clinically relevant changes were found in any of the laboratory or other assessments in these two patients or any patient in the study.

Median total insulin antibody level increased in the AERx group (from 6 to 35% trace binding of total) but remained unchanged in the SC group (10 to 9%) throughout the trial. No correlation was

Table 2—*Mean PFT values at baseline and the end of the trial*

	AERx		SC	
PFT	Baseline	End of trial	Baseline	End of trial
n	54	50	53	48
FVC	95.6 ± 12.7	93.9 ± 14.2	97.2 ± 13.7	95.3 ± 14.4
Change from baseline analysis	−2.3 ± 5.7		−2.4 ± 5.8	
	AERx minus SC: 0.19 [−2.0 to 2.43], $P = 0.86$			
n	54	50	53	48
FEV1	97.6 ± 13.2	95.1 ± 14.4	96.2 ± 12.2	93.4 ± 13.9
Change from baseline analysis	−3.2 ± 5.7		−3.5 ± 5.8	
	AERx minus SC: 0.36 [−1.9 to 2.62], $P = 0.75$			
n	54	50	53	48
FEV1%	104.6 ± 8.6	103.9 ± 9.6	101.1 ± 8.3	100.1 ± 10.0
Change from baseline analysis	−1.1 ± 5.4		−2.1 ± 5.8	
	AERx minus SC: 1.07 [−1.1 to 3.28], $P = 0.34$			
n	51	49	53	48
TLC	94.5 ± 13.4	93.4 ± 13.2	96.1 ± 12.9	96.1 ± 13.8
Change from baseline analysis	−1.9 ± 6.0		−0.86 ± 6.0	
	AERx minus SC: −1.08 [−3.5 to 1.30], $P = 0.37$			
n	53	49	52	48
DLCO	91.3 ± 16.8	90.8 ± 18.4	93.6 ± 16.7	94.3 ± 16.5
Change from baseline analysis	−2.0 ± 9.1		−1.1 ± 8.9	
	AERx minus SC: −0.97 [−4.5 to 2.52], $P = 0.58$			

Data are means ± SD unless otherwise indicated. The calculated mean difference of change from baseline after 12 weeks of treatment, the 95% CI, and *P* values are based on an ANOVA. The PFT values measured were as follows: forced vital capacity (FVC), forced expiratory volume in first second (FEV1), forced expiratory volume in first second/FVC (FEV%), total lung capacity (TLC), and diffusion capacity for carbon monoxide (DLCO). The unit for all these values was percent of predicted normal value.

found between change in total insulin antibody level, metabolic control, and insulin dose. IgG antibody levels showed a substantial increase in five subjects in the AERx group, but median levels only increased slightly. Small increases in IgE antibodies were seen in four patients in the AERx group and one patient in the SC group during the trial. Median IgA antibody levels decreased in both groups during the trial. Out of the five patients with increased IgG levels at the end of the trial, three patients had a higher value and two patients had a lower value than the median at the start of the study. No clinical signs or symptoms were reported with the changes in antibodies.

Verified nonrecoverable malfunctions of the AERx iDMS device were found in 3% of the devices used in the trial. There were slightly more contacts per patient involving instruction time in the AERx group compared with the SC group (mean difference 1.67). In addition, the mean instruction time per contact (in minutes) was slightly higher for the AERx group (mean difference 5.38). The majority of (unscheduled) telephone contacts occurred in the first month for both treatment groups. Few patients in either the AERx or SC group experienced any "sick leave" days (6 vs. 8). A total of 21 patients in the AERx group used escape medication on any occasion over the 12-week period, and no patients used it for >5% of prescribed medications.

CONCLUSIONS — It is well established that intensification of insulin regimens can improve glycemic control and thereby reduce the risk of developing diabetic complications (14–16). However, intensified insulin regimens are challenging and require daily multiple injections. In one study of 115 insulin-treated patients with type 1 or 2 diabetes, 70% did not wish to take more than one or two injections per day, whereas 45% admitted to avoiding or omitting injections and 28% suffered high injection-anxiety scores (7). In the 1920s, Gänsslen (17) and Heubner et al. (18) were the first to demonstrate considerable success in reducing blood glucose levels after insulin inhalation and, because of drawbacks with other modes of delivery, such as dermal, oral, or nasal (19,20), it now appears that inhaled insulin will be the first available alternative to injection (21).

The present trial demonstrates that in patients with type 2 diabetes, inhaled fast-acting human insulin immediately before meals via the AERx iDMS results in similar long-term metabolic control as SC human insulin administered 30 min before meals in an intensive insulin regimen. These results provide clinical proof of concept for inhaled insulin via AERx iDMS.

An unexpected finding in the present study was that FSG was significantly lower in the AERx group than in the SC group after 12 weeks of treatment. However, there was no statistically significant difference in the home-measured FBG between the two groups. There was no difference in the NPH doses between the two groups. Because the study was not designed specifically to measure FSG, further investigation will be needed before

drawing a firm conclusion from this finding.

The ratio observed for mealtime insulin in the AERx group showed that one AERx unit corresponds to ~1 IU of SC insulin. Naturally, all doses need to be titrated on an individual basis, and there was clearly no reluctance to increase the insulin dose in the AERx group to reach target, because the decrease in HbA_{1c} was similar to that in the SC group. The intrasubject variability for the AERx group was as good as that in the SC group. This reassuring finding, as it could be expected that higher variability would be seen with an inhaled insulin device, is supported by a pharmacokinetic and pharmacodynamic study that demonstrated similar or lower intrasubject variability with AERx iDMS compared with SC insulin administration (22).

It is also encouraging to note that there were no differences of frequency or type of adverse events between the AERx and SC groups and that further follow-up tests in the two cases of decreased pulmonary function in the AERx group showed that PFT values returned toward normal after the trial, and there were no clinical signs or symptoms accompanying these changes. It is likely that physicians were less aware about possible decreases in PFT in the SC group than in the AERx group. These findings do not indicate any difference in pulmonary function between the two treatment forms. However, pulmonary function should be closely monitored in future long-term trials.

The increase in antibodies in this study is consistent with those seen in long-term insulin analog trials where no effects on efficacy and safety could be attributed to changes in antibody levels (23,24). Increased insulin antibody serum binding, with no apparent clinical changes, has also been observed with another inhaled insulin device (25,26), as well as with treatment with implantable insulin pumps (27).

In the present study, no clinical signs or symptoms were reported in connection with the changes in antibodies and no correlation between change in total insulin antibody level and metabolic control or insulin doses was found. Because little information regarding the relationship between inhaled insulin and total and insulin-specific antibodies is available, further investigation is needed to interpret these results, and insulin antibody levels should be monitored in forthcoming studies.

Three major hypoglycemic episodes were reported in the AERx group; two occurred in a patient with a history of major hypoglycemic episodes, and the third was caused by a patient administering inhaled insulin but omitting a meal. Numerically fewer total hypoglycemic events occurred in the AERx group compared with the SC group. Overall, therefore, inhaled insulin did not appear to be associated with an increased risk of hypoglycemia compared with SC insulin, and no major safety issues arose. Inhaled insulin via the AERx iDMS was considered well tolerated.

In conclusion, this trial demonstrates similar efficacy and safety without higher variability of intensified insulin treatment between inhaled insulin via AERx iDMS and SC insulin injections. Thereby, proof of concept is established for the AERx iDMS. Further studies are needed to specifically investigate the long-term safety of this system as well as expected benefits of AERx iDMS, such as increased patient satisfaction, better glycemic control, and compliance with patients progressing to insulin or intensifying treatment.

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