

Intrasubject Variability of Inhaled Insulin in Type 1 Diabetes: A Comparison with Subcutaneous Insulin

CHRISTOPH KAPITZA, M.D.,¹ MARCUS HOMPECH, M.D.,¹
BIRGITTE SCHARLING, B.Sc.,² and TIM HEISE, M.D.¹

ABSTRACT

We compared intrasubject variability of insulin and glucose profiles after a standardized meal between insulin inhaled via the AERx[®] insulin Diabetes Management System (AERx iDMS, Aradigm Corp., Hayward, CA) and given as a subcutaneous injection. In this single-center, parallel, randomized, open-labeled trial, 17 male, non-smoking patients with type 1 diabetes (mean age, 27.7 years; body mass index, 23.4 kg/m²) received a fixed, individualized dose of human insulin, on four treatment days followed by an individualized breakfast, administered either by inhalation via AERx iDMS ($n = 9$) or by subcutaneous injection. Serum insulin and serum glucose levels were determined at regular intervals for 6 h postdose. Intrasubject variability was expressed as coefficient of variation. No statistically significant differences in intrasubject variability were observed between the treatments for the areas under the insulin curves for 0–6 h [27% vs. 19% (inhaled insulin vs. subcutaneous)] and areas under the glucose curves 0–6 h (30% vs. 23%). Intrasubject variability values for insulin half-life, terminal elimination rate constant, and mean residence time were significantly less in the inhaled insulin group compared with the subcutaneous insulin group ($P = 0.01$ – 0.02). Only one potentially trial product-related adverse event (an audible wheeze) was reported, and no clinically relevant changes in pulmonary function were detected. The intrasubject variability was comparable between patients receiving inhaled insulin and subcutaneous insulin, thereby confirming the reproducibility of administering insulin via AERx iDMS. Inhaled insulin was well tolerated and is a feasible alternative to subcutaneous insulin in patients with type 1 diabetes.

INTRODUCTION

INTENSIFIED INSULIN THERAPY is considered imperative if optimal glycemic control is to be achieved in patients with type 1 diabetes. The landmark study by the Diabetes Control and Complications Trial group¹ demonstrated that tight glycemic control dramatically reduces the

risk of late complications compared with suboptimal blood glucose control. Superior glyce-mic control can be achieved using intensive therapy (three or more insulin injections per day), compared with conventional therapy (two injections per day); however, the invasiveness and inconvenience of multiple injection regimens can often impede compliance.

¹Profil Institute for Metabolic Research, Neuss, Germany.

²Novo Nordisk A/S, Copenhagen, Denmark.

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An additional obstacle facing patients and physicians when trying to achieve well-controlled blood glucose levels is the unpredictable response to identical doses of insulin. Individual titration is an important way to reduce the variation seen between patients (intersubject variability); however, problems can arise on a day-to-day basis within an individual (intrasubject variability). Unexpected insulin patterns and, hence, blood glucose levels prevent tight glycemic control from being achieved, increase the risk of hypoglycemia, and, in the long run, increase the risk of diabetes-related complications.

Alternative delivery routes are currently being researched in order to overcome issues of compliance and variability.² The AERx[®] insulin Diabetes Management System (AERx iDMS, Aradigm Corp., Hayward, CA) is an inhalation-activated system with insulin strips, developed to enable aerosols of mealtime bolus liquid insulin to be delivered into the deep lung. AERx iDMS emits a fine particle aerosol (mass median aerodynamic diameter, 2.5 μm ; geometric standard deviation, 1.3) from single-use insulin strips by extruding the prepacked solution through hundreds of precisely laser-ablated holes in a single-use nozzle. AERx iDMS has been designed to guide the patient through the inhalation maneuver via "Breath Check," which ensures reproducible delivery of the insulin aerosol to the deep lung by release of particles only when flow rate and inspired volume are optimal.³ Recently, the AERx iDMS has demonstrated efficacy and safety comparable to those of subcutaneous insulin in patients with type 2 diabetes.⁴

The intrasubject variability of the metabolic response when using inhaled powdered insulin is purportedly similar to that achieved when administering subcutaneous insulin injections.⁵⁻⁸ A previous study has specifically examined intrasubject variability of pharmacokinetic and pharmacodynamic parameters using an aerosol of liquid insulin, and found that inhaled dosing exhibits reproducibility comparable to that of subcutaneous insulin.⁷ However, particle-size distribution and inspiratory flow rates are among the variables that may influence reproducible delivery,³ and therefore the intrasubject variability of the AERx iDMS should also be determined.

The aim of this study was to investigate the intrasubject variability of insulin and glucose serum profiles in patients with type 1 diabetes using inhaled liquid insulin, compared with those receiving subcutaneous insulin injections. In contrast to previous studies employing the glucose-clamp technique this study was focused on the variability in postprandial blood glucose excursions, which is the clinically most relevant parameter for a prandial insulin.

A preliminary abstract of this work has been published previously.⁹

PATIENTS AND METHODS

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

Study participants

This was a single-center, parallel, randomized, open-labeled trial in 17 male patients with type 1 diabetes [mean $\pm$ SD: age 27.7 ± 5.3 years, body mass index (BMI) 23.4 ± 2.5 kg/m²]. All participants had received human insulin treatment for at least 12 months prior to screening, and hemoglobin A_{1c} (HbA_{1c}) levels were $\leq 11\%$. Patients were non-smokers for ≥ 12 months, which was confirmed by negative urine cotinine, and all had normal lung function [forced vital capacity (FVC) and forced expiratory volume in the first second (FEV₁) were $\geq 85\%$ of predicted normal values].

Study protocol

After the initial screening visit, patients were dosed on four different treatment days, which were separated by a washout period of no longer than 14 days. On the first treatment day, patients (who fasted overnight) were randomized to receive a single dose of human insulin administered either by the current version of AERx iDMS or as a subcutaneous injection, before an individualized breakfast, i.e., each subject chose his own breakfast in accordance with individual eating habits. Breakfast remained the same for each subject on all four dosing days.

The insulin dose was individually determined, based on each patient's usual preprandial morning dose, and this dose was fixed for each of the subsequent treatment visits. The mean dose was 0.12 ± 0.4 AERx units and 0.13 ± 0.06 IU/kg of body weight (absolute doses: 9.8 ± 3.4 AERx units vs. 10.0 ± 4.5 IU). Patients who received subcutaneous insulin were always injected by trained personnel, who adopted the same procedure for each randomized patient: subcutaneous injection of human soluble insulin Actrapid® HM (Novo Nordisk A/S, Bagsvaerd, Denmark) approximately half an hour before breakfast via a NovoPen® 3 injector (Novo Nordisk A/S), into a lifted skinfold in the lower right abdominal quadrant. Patients who were allocated to receive inhaled insulin were dosed just prior to breakfast with a single dose of inhaled human insulin (1–2 inhalations) from a solution in disposable insulin strips administered via AERx iDMS. One AERx unit (260 μ g of insulin) provides approximately the same glucose-lowering effect as 1 IU of subcutaneous insulin¹⁰; therefore, the same number of AERx units as IU units was selected for each inhaled dose. A disposable insulin strip contained the equivalent of 10 subcutaneous units. Patients did not receive NPH insulin in the morning of the treatment days.

Serum glucose and serum insulin concentrations were measured at regular intervals for 6 h following insulin administration in order to determine pharmacokinetic and pharmacodynamic end points (see statistical analysis below).

Safety

Safety was evaluated throughout the study period, and adverse events and hypoglycemic episodes were assessed at each treatment visit. Pulmonary function tests (FVC and FEV₁), blood pressure, and heart rate were also measured on each treatment day before dosing and 6 h postdose. Physical examinations and laboratory tests (including hematology, biochemistry, urinalysis, and electrocardiogram) were performed at screening and at the end of the final treatment visit.

Statistical analysis

All 17 patients completed the trial and were included in the analyses of pharmacokinetic

and pharmacodynamic end points. The primary pharmacokinetic end point was the area under the serum insulin profile in 6 h postdose [AUC_{ins} (0–6 h)]. Secondary end points (pharmacokinetic) were maximal serum insulin concentration ($C_{\max, \text{ins}}$), time to maximal serum insulin concentration ($t_{\max, \text{ins}}$), mean residence time of insulin (MRT), insulin half-life ($t_{1/2}$), terminal elimination rate constant (λ_z), and initial rate of increase. Other secondary end points (pharmacodynamic) included the area under the serum glucose profile in 6 h postdose [AUC_{glu} (0–6 h)], maximal serum glucose concentration ($C_{\max, \text{glu}}$), and time to maximal serum glucose concentration ($t_{\max, \text{glu}}$), and were determined from the serum glucose concentration curves. All area under the curve values were calculated using the trapezoidal method. The estimated coefficient of variation (CV%) for each end point was calculated as an estimate of intrasubject variability within the two treatment groups, and a separate analysis of variance model was applied to each of the two treatments. The safety evaluation was based on all patients exposed to the trial product ($n = 17$).

The sample size calculation was based on the comparison of the two treatments with respect to intrasubject variability, i.e., the total variation for one subject from one profile to the next profile. With 16 subjects and four replications per subject the study was powered to detect a difference in the ratio of standard deviations (as parameter for variability) between the treatments of less than 0.5 or more than 2.0 with 91% probability at a 5% significance level. It was planned to enroll 18 subjects in order to ensure 16 subjects to complete the trial.

RESULTS

Demographics

Patient characteristics are shown in Table 1. The two treatment groups were comparable with regards to age, BMI, HbA_{1c}, and pulmonary function.

Intrasubject variability

Intrasubject variability for each parameter tested is shown in Table 2. There was no sta-

TABLE 1. PATIENT CHARACTERISTICS AT THE SCREENING VISIT

	AERx iDMS	Subcutaneous
Number	9	8
Age (years)	28.0 (21.8–37.8)	27.4 (21.4–32.4)
BMI (kg/m ²)	23.0 (19.6–28.2)	23.8 (21.1–26.4)
HbA _{1c} (%)	7.8 ± 1.0	7.6 ± 0.4
C-peptide (nmol/L)	0.07 ± 0.1	0.04 ± 0.0
% of normal, predicted value		
FEV ₁	102.1 ± 9.0	107.0 ± 12.4
FVC	98.3 ± 7.6	104.4 ± 14.3

All values are shown as the mean ± standard deviation except for age and BMI, which are shown with the range.

tistically significant difference in intrasubject variability of AUC_{ins} (0–6 h) in patients receiving inhaled insulin compared with those in the subcutaneous insulin treatment group (CV 27% vs. CV 19%, respectively) (Fig. 1). There was also no statistical significant difference in intrasubject variability between the treatment groups in terms of $C_{\max, \text{ins}}$, $t_{\max, \text{ins}}$, and initial rate of increase of insulin. The λ_z , MRT, and $t_{1/2}$ end points did, however, show significantly less ($P = 0.01$, $P = 0.02$, and $P = 0.01$, respectively) intrasubject variability in patients using AERx iDMS compared with those receiving subcutaneous insulin (Table 2).

Of the secondary pharmacodynamic end points determined [AUC_{glu} (0–6 h), $C_{\max, \text{glu}}$, and $t_{\max, \text{glu}}$], there was no difference in intrasubject variability between patients receiving insulin via either the pulmonary route or subcutaneously.

Actual values for the pharmacokinetic and pharmacodynamic end points measured are shown in Table 3. As the trial was designed and powered to examine intrasubject variability, no

statistical analysis was performed to compare the efficacy of the two treatments.

Safety

Throughout the study period, only one mild adverse event (an audible wheeze) was reported (pulmonary treatment group) and was considered as possibly related to the trial treatment. No action was taken, and the adverse event spontaneously disappeared after 6 days. One hypoglycemic episode was reported (subcutaneous treatment group). There were no clinically relevant changes in vital signs, pulmonary function tests, physical examinations, electrocardiograms, or standard safety laboratory parameters at the end of the study, in either of the two treatment groups.

DISCUSSION

This study investigated the reproducibility of inhaled liquid human insulin, delivered by the innovative AERx iDMS, compared with

TABLE 2. INTRASUBJECT CV FOR PHARMACOKINETIC AND PHARMACODYNAMIC END POINTS

End point	Intrasubject CV (%)				
	AERx iDMS	Subcutaneous	AERx iDMS/subcutaneous ratio	95% confidence interval	P value
AUC _{ins} (0–6 h) (mU/L × h)	27	19	1.47	0.87; 2.45	0.15
$C_{\max, \text{ins}}$ (mU/L)	23	22	1.03	0.64; 1.62	0.90
$t_{\max, \text{ins}}$ (min)	72	59	1.23	0.77; 1.93	0.38
Initial rate of increase (mU/L × h)	26	39	0.67	0.42; 1.05	0.08
λ_z (1,000/min)	22	40	0.55	0.34; 0.87	0.01
MRT (min)	20	34	0.59	0.37; 0.92	0.02
$t_{1/2}$ (min)	22	40	0.55	0.34; 0.87	0.01
AUC _{glu} (0–6 h)	30	23	1.29	0.84; 1.98	0.24
$C_{\max, \text{glu}}$ (mU/L)	23	22	1.02	0.66; 1.56	0.93
$t_{\max, \text{glu}}$ (min)	46	64	0.71	0.45; 1.10	0.12

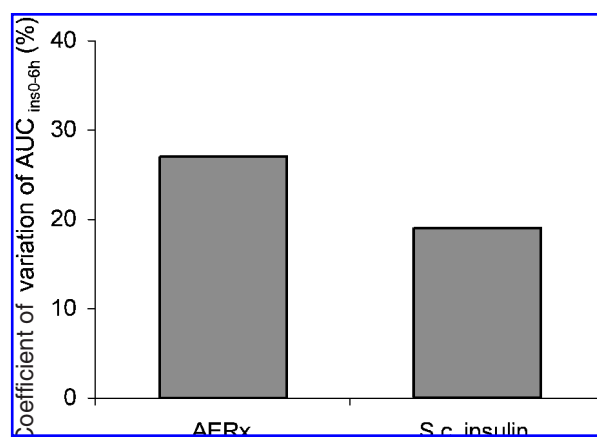


FIG. 1. Intrasubject variability (CV%) of area under the serum insulin profile (0–6 h) after either inhaled insulin, administered via AERx iDMS, or subcutaneous (S.c.) insulin.

that of subcutaneous human insulin. There was no statistically significant difference in the intrasubject variability of the main outcome parameter AUC_{ins} (0–6 h) between patients using inhaled insulin (CV 27%) compared with those receiving subcutaneous insulin (CV 19%). The current study, therefore, provides supporting evidence of good reproducibility when using the AERx iDMS that is comparable to subcutaneous insulin. The estimates of intrasubject variability in this study are considered reliable, as each patient received the same dose of insulin using the same method and device on each of the four treatment days.

The values for intrasubject variability of inhaled insulin obtained in this study are comparable to those previously reported from subcutaneous human insulin absorption studies,

where CV reached 35%.¹¹ Intrasubject variability demonstrated in the current study also compares well with that reported for inhalation of powdered insulin; however, this study used a vehicle that acted as an absorption enhancer (CV 15%).¹² A further study by Brunner et al.¹³ demonstrated intrasubject variability for insulin serum profiles using the AERx iDMS to be 26%; however, it should be noted that intrasubject variability rates calculated in that study were from serum insulin profiles over 10 h and not 6 h, as in the current study. Furthermore, the CV calculated in the aforementioned study was done so using different doses of insulin, and there were no repetitions of the same dose in a single subject during the study.

Despite intrasubject variability being a familiar and burdensome issue to patients and diabetologists alike, there are relatively few studies that address the problem. Indeed, the methodologies of trials that do examine intrasubject variability are limited as often, only one dose of insulin is replicated for the calculation of CV.^{11,14} Furthermore, a number of variability studies are carried out using healthy volunteers, and therefore comparisons with variability in patients with diabetes should be made with caution.

There was no statistically significant difference in intrasubject variability of the pharmacokinetic end points C_{max} , t_{max} , and initial rate of increase between the two treatment groups. However, for MRT, λ_z , and $t_{1/2}$, the intrasubject variability was significantly lower with inhaled insulin compared with subcutaneous insulin. The MRT value is calculated from all

TABLE 3. PHARMACOKINETIC AND PHARMACODYNAMIC END POINT

End point	Mean $\pm$ SD value	
	AERx iDMS	Subcutaneous
AUC _{ins} (0–6 h) (mU/L $\times$ h)	135 $\pm$ 61	143 $\pm$ 57
$C_{max,ins}$ (mU/L)	40.7 $\pm$ 7.2	38.2 $\pm$ 6.0
$t_{max,ins}$ (min)	79 $\pm$ 35	102 $\pm$ 48
Initial rate of increase (mU/L $\times$ h)	2.4 $\pm$ 0.0	1.7 $\pm$ 0.0
λ_z (1,000/min)	4.0 $\pm$ 0.0	4.9 $\pm$ 0.1
MRT (min)	302 $\pm$ 365	339 $\pm$ 681
$t_{1/2}$ (min)	195 $\pm$ 173	210 $\pm$ 310
AUC _{glu} (0–6 h) (mU/L $\times$ h)	93 $\pm$ 23	80 $\pm$ 19
$C_{max,glu}$ (mU/L)	19.4 $\pm$ 0.9	17.3 $\pm$ 0.8
$t_{max,glu}$ (min)	135 $\pm$ 76	176 $\pm$ 200

serum insulin concentrations, rather than the single maximum value, and may therefore represent a better estimate of the absorption of insulin than $C_{\max}$. A possible explanation for the significant differences in variability between the two treatment groups is that the $t_{\max, \text{ins}}$ is less when insulin is administered via the pulmonary route rather than subcutaneously. The more rapid onset of action of inhaled insulin¹⁰ provides less opportunity for variation when assessing the intrasubject variability of MRT, λ_z , and $t_{1/2}$ end points. The apparently high rate of intrasubject variability for $t_{\max, \text{ins}}$ in patients receiving inhaled (and subcutaneous) insulin is not unexpected. High absorption rates have been previously demonstrated¹⁵ and are not necessarily associated with increases in insulin action. Lower intrasubject variability for $t_{\max, \text{gluc}}$ in both treatment groups, supports this.

The results obtained for the pharmacodynamic end points in this study compare well with intrasubject variability reported for total glucose infusion in a previous study in healthy volunteers (CV 22.6%).¹⁴ It may be thought that inhaled insulin should have been compared with short-acting insulin analogues like insulin aspart or insulin lispro, since today many patients with type 1 diabetes are using fast-acting insulin analogues as their bolus insulin. However, it should be noted that this might have led to lower postprandial blood glucose values, but most probably not to substantially different values for intrasubject or intersubject variability. A previous study comparing the variability in the metabolic action between insulin aspart and regular insulin did not observe any significant differences between these two compounds.¹⁶ Therefore, this first study was performed as a comparison of like with like (human insulin with human insulin). Future studies should address the comparison with short-acting analogues.

Assessments carried out in the current study did not reveal any major safety issues, and inhaled insulin was well tolerated. Only one adverse event with a possible relation to inhaled insulin was reported: An audible wheeze was apparent at the end-of-study physical examination. At a follow-up examination, 6 days later, the wheeze had spontaneously disap-

peared. There were no other clinically relevant changes in laboratory assessments, vital signs, or pulmonary function tests. Previous AERx iDMS studies have not raised any safety concerns,^{13,15} and inhaled insulin is considered to be well tolerated.

There are many factors that affect intrasubject variability, including preparation and mixing of insulins, injection site and technique, choice of syringe and needle, and subcutaneous blood flow.¹⁷⁻¹⁹ Although a number of these parameters can be immediately avoided when administering insulin via the pulmonary route, thereby reducing the risk of variability, inhaled insulin would obviously have its own intrinsic parameters and variables, and these should be fully investigated.

In summary, despite the reported benefits of good glycemic control,¹ intensive insulin therapy is not acceptable for many patients because of painful and inconvenient daily injections. Inhaled insulin offers a noninvasive yet efficient alternative route of delivery,²⁰ which is well accepted by patients with diabetes. Indeed, a recent report confirmed that patients were significantly more satisfied with inhaled insulin therapy compared with the conventional subcutaneous insulin regimen.²¹ The current study highlights the reproducibility, and hence predictability, regarding both the extent and rate of insulin absorption of the AERx iDMS in the delivery of inhaled insulin in patients with type 1 diabetes.

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Address reprint requests to:

Tim Heise, M.D.

Profil Institute for Metabolic Research

Hellersbergstrasse 9

D-41460 Neuss, Germany

E-mail: tim.heise@profil-research.de

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