

Dose-Response Relationships of Inhaled Insulin Delivered via the Aerodose Insulin Inhaler and Subcutaneously Injected Insulin in Patients With Type 2 Diabetes

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OBJECTIVE — To compare the dose-response relationship following inhalation of regular insulin delivered via the Aerodose insulin inhaler with that following subcutaneously injected regular insulin in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Twenty-four patients with type 2 diabetes (21 nonsmoking men, aged 36–80 years) each received two of three doses of 80, 160, or 240 units inhaled regular insulin, delivered via a clinical Aerodose insulin inhaler, and two of three corresponding doses of 8, 16, or 24 units by subcutaneous injection under isoglycemic clamp conditions on 4 separate study days in an incomplete block design study. Glucose infusion rates (GIRs) and serum insulin concentrations were monitored over the following 8 h.

RESULTS — Inhaled insulin exhibited significantly shorter time-to-peak insulin levels (T_{\max} 77 ± 66 vs. 193 ± 104 min, $P < 0.001$) and time-to-peak metabolic effects (T_{GIRmax} 240 ± 94 vs. 353 ± 60 min, $P < 0.001$) compared with subcutaneously injected insulin. Comparison of total insulin absorption (insulin area under the curve [AUC]) versus total metabolic effect (GIR-AUC) from 0 to 8 h (group means) revealed overlapping dose-response relationships for both inhaled and subcutaneous injection treatments. Comparison of slopes revealed no significant differences between the inhaled and subcutaneous injection treatment groups ($P = 0.6$). No significant differences in either relative bioavailability or relative biopotency were found among doses, indicating a consistent subcutaneous injection-to-inhaled dosing conversion ratio among doses. No serious adverse events or clinically relevant changes in lung function were observed.

CONCLUSIONS — The overlapping dose-response curves of inhaled and subcutaneous treatments together with a consistent relative bioavailability and relative biopotency for inhaled insulin across doses suggest that the Aerodose insulin inhaler will deliver a pharmacologically predictable insulin dose to patients with diabetes similar to that observed following subcutaneous injection.

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Abbreviations: AUC, area under the curve; GIR, glucose infusion rate.

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

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Demonstrating that inhaled insulin can be titrated similar to subcutaneous injection is an important prerequisite to showing the clinical viability of this novel mode of insulin delivery. Although several specialized aerosol delivery systems are currently in various stages of development for pulmonary delivery of insulin (1–3), a head-to-head comparison of the dose response of inhaled and subcutaneously injected insulin has not been reported. The Aerodose insulin inhaler is developed to deliver aerosolized liquid insulin to meet the preprandial insulin needs of patients with diabetes. The aim of the present study was, therefore, to compare the dose-response relationship of inhaled and subcutaneously injected insulin and to determine the resulting inhalation-to-subcutaneous injection conversion ratio across three doses in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A single-center, open-label, randomized, active-controlled, crossover study was conducted in patients with type 2 diabetes. The protocol was approved by the University of California Human Research Protections Program, and written informed consent was obtained before trial procedures. The study design used a four-treatment, four-period, four-sequence, balanced crossover design in which each patient received two of three subcutaneously injected doses of insulin—low (8 units), medium (16 units), or high (24 units)—and two of three corresponding inhaled doses of insulin—low (80 units), medium (160 units), or high (240 units)—on 4 separate study days. This design enabled eight subjects to receive two doses of both inhaled and subcutaneously injected insulin. The inhaled dose was scaled up 10-fold in comparison to subcutaneous injection based on a relative bioavailabil-

ity for inhaled insulin of ~10% observed in previous studies (4,5).

Twenty-six patients with type 2 diabetes were enrolled in the study and 24 completed the study. One patient was withdrawn because he had participated in another investigative drug study in the previous 3 months, and a second patient withdrew consent for personal reasons. Both patients had received a single subcutaneously injected dose before withdrawal. Data from these two patients are not included in the present dataset. Twenty-one men and three women completed the study; they ranged in age from 36 to 80 years, were nonsmokers, had normal lung function at screening (FEV_1 3.2 ± 0.4 l [mean \pm SE], $93 \pm 7\%$ of predicted value), and were insulin treatment-naïve. Patients had a BMI of 29.6 ± 2.8 kg/m² with 8 patients classified as obese (BMI 30–35 kg/m²) and 15 as overweight (BMI 25–30). The mean duration of type 2 diabetes diagnosis was 8.3 ± 6.9 years (range 1–33 years), and at screening, patients had a mean HbA_{1c} of $7.5 \pm 0.96\%$ and fasting blood glucose of 145 ± 0.28 mg/dl (range 94–210). At screening, all study candidates were tested for their ability to perform a 5-s slow deep breath followed by a 5-s breath-hold breathing maneuver required for dosing via the Aerodose insulin inhaler. Recordings of flow rate versus time obtained from inhalations through a model Aerodose insulin inhaler attached to a spirometer and software program (2120 Spirometer and Spirotach IV software; Vitalograph, Lenexa, KS) showed that all screened subjects were able to perform the breathing maneuver.

Patients on oral antidiabetic agents stopped their medication after the morning dose on the day before each study day. Patients were admitted into the inpatient clinical research unit at ~1800 h on the evening before each treatment day. A follow-up medical history was taken, and any concomitant medications were recorded. Patients were provided with a standardized meal containing 40–50% carbohydrates, 25–35% fat, and 10–20% protein, which was entirely consumed by 2000 h. Subsequently, patients fasted overnight, except for water, and until at least 8 h after dosing with insulin the next day. Subjects were asked to refrain from excessive physical activity for 24 h before each study day. Alcohol intake was prohibited until the time of discharge the fol-

lowing day. On the morning of the study day, patients were again tested for their ability to perform the breathing maneuver described above. Before dosing, each patient had an antecubital venous catheter inserted into the right arm for the infusion of dextrose and a retrograde ipsilateral hand vein catheter placed in a warming device for the drawing of arterial blood samples for the measurement of glucose, insulin, and C-peptide levels.

Following catheterization, an isoglycemic clamp was established at that day's baseline value. Fasting blood glucose was measured at -45 , -30 , and -15 min before insulin dosing, and the mean of these three measurements was used as the target clamp glucose level. If the mean fasting blood glucose was <90 mg/dl, subjects were not dosed with insulin but asked to return to the clinic on another day. If fasting blood glucose was ≥ 90 mg/dl, subjects were dosed with either inhaled or subcutaneously injected insulin according to the randomization schedule. At -2 h and -30 min before study drug administration, vital signs and spirometry measurements were taken, and at the end of the baseline period, patients were dosed with inhaled or subcutaneously injected insulin. Each patient was dosed on 4 separate study days with two inhaled and two subcutaneously injected doses. Thus, on 2 of 4 study days, patients inhaled insulin (Humulin R, U-500; Eli Lilly, Indianapolis, IN) delivered via the Aerodose insulin inhaler, and on the other 2 study days, a subcutaneous injection of regular insulin (Humulin R, U-100; Eli Lilly) was administered by a physician in the patient's anterior abdominal wall by syringe (Microfine 4+; Becton-Dickinson, Franklin Lakes, NJ).

After dosing (end of dosing was defined as $t = 0$ min), blood glucose was monitored every 5 min for the first 6 h postdosing and then every 10 min for the following 2 h. Glucose (20% solution) infusion rate (GIR) was adjusted, as necessary, to maintain plasma glucose at the target fasting glucose level for the 8 h of the isoglycemic clamp study. Blood samples for serum insulin measurements were collected via the indwelling catheter at -45 , -30 , and -15 min predosing, at 0, 5, 10, 20, 30, 40, 50, and 60 min, and every 30 min to 8 h postdosing. Samples for plasma C-peptide measurements were taken at -30 , -15 , and -5 min predosing, at 0, 5, 10, 20, 30, 40, 50, and 60

min, every 30 min to 7 h, and at 8 h postdosing. Serum insulin concentrations were measured using a radioimmunoassay kit (DPC-Biermann, Bad Nauheim, Germany) (mean intra- and interassay coefficient of variation [CV] 6.0 and 3.5%, respectively). Plasma C-peptide was measured using a human C-peptide radioimmunoassay kit (Linco Research, St. Charles, MO) (mean intra- and interassay CV 4.8 and 12.3%, respectively). Radioimmunoassays were performed at the Institut für Klinische Forschung und Entwicklung (IKFE) (Mainz, Germany).

Spirometry measurements (FEV_1 and FVC, average of two measurements) were taken at ~1 h and 30 min before study drug administration and at 1 and 6 h postdosing. A $\pm 10\%$ change in FEV_1 or FVC was considered a clinically relevant change in these measurements. An electrocardiogram was recorded at ~2 h before study drug administration. Vital signs were taken at time points -2 , 0.5, 4, and 8 h, and blood pressure was monitored by automatic cuff every 30 min for the first 2 h postdosing. After completion of the 8-h clamp period, subjects were given a full meal and plasma glucose was monitored at 8.5 and 9 h postdosing. Patients were discharged after they were determined to be clinically stable and returned to the research unit for subsequent treatments following intervals of 3–20 days.

Aerodose insulin inhaler

The clinical Aerodose insulin inhaler used in this study has been previously described (6). Briefly, this device is a small handheld breath-actuated inhaler that contains Aerogen's electronic aerosol generator. When liquid is placed onto the aerosol generator, a micropumping action creates a fine-droplet low-velocity aerosol that is suited for deep lung delivery (7). Vibration of the aerosol generator is triggered by an inspiratory flow rate >15 l/min. The Aerodose insulin inhalers used in this study delivered aerosol with a mean droplet size of 3.7 ± 0.13 μ m volume median diameter and were configured to deliver aerosol during the first 4 s of each 5-s inhalation. The low, medium, and high inhalation doses were delivered with a mean of 5, 11, and 17 5-s slow deep inhalations, respectively. The lack of strict proportionality between breath number and increasing dose is the result of a greater opportunity for an occasional

short (<4-s) inhalation, which requires extra breaths to complete the dose, at the higher doses.

Statistical analysis

The SAS procedure PROC GLM was used for statistical analyses in this study. All statistical tests were performed against a two-sided alternative hypothesis, with a significance level of 5% ($\alpha = 0.05$). After correction for baseline, a polynomial function (sixth order) was fitted to each individual GIR profile obtained for estimation of pharmacodynamic summary measures. Baseline GIR was calculated as the mean of all GIRs recorded for the 2 h preceding insulin dosing. Serum insulin was also corrected for baseline.

An ANOVA model, including period, treatment, sequence, and within-subject sequence factors, was used to compare all of the pharmacokinetic and pharmacodynamic parameters. For analysis of the area under the curve (AUC), C_{max} , and GIR_{max} values, the data were transformed using the natural logarithm transformation before analysis. At each dose level, the relative bioavailability and biopotency were calculated from the ratio of the AUC values (insulin-AUC and GIR-AUC, respectively) for inhaled doses relative to those subcutaneously injected, normalized to the dose $[(AUC_{INH}/AUC_{SC}) \times (Dose_{SC}/Dose_{INH}) \times 100]$.

The primary null hypothesis tested in this study was that the difference in the mean relative bioavailability and biopotency of insulin between the three dose levels was equal to zero ($H_0: \mu_{low} = \mu_{medium} = \mu_{high}$), where μ_{low} , μ_{medium} , and μ_{high} represent the mean relative bioavailability or biopotency at the low, medium, and high doses, respectively.

In addition to the test of the treatment effect, the linearity of the dose-response relationship for the two treatment groups (inhalation and subcutaneous injection) was tested. A covariance model that tested for any interaction between the treatments (inhalation or subcutaneous injection) and the x-axis variable (insulin-AUC) was used to evaluate the differences in slope between inhaled and subcutaneously injected treatments.

RESULTS

Pharmacokinetics

Serum insulin concentrations following dosing with low, medium, and high doses

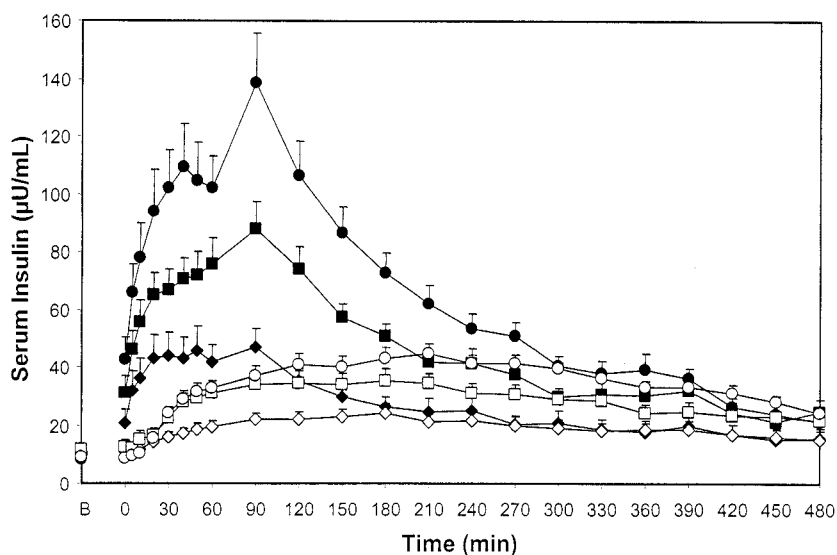


Figure 1—Changes in serum insulin levels over 8 h following administration of inhaled insulin (◆, 80 units; ■, 160 units; ●, 240 units) and subcutaneous injection (◇, 8 units; □, 16 units; ○, 24 units) in patients with type 2 diabetes. The mean of baseline values is also shown (time point B). Data points are means \pm SE ($n = 16$) at each time point for low, medium, and high doses for inhaled and injected insulin.

of inhaled and subcutaneously injected insulin are shown in Fig. 1 and Table 1. Serum insulin levels before exogenous insulin administration were similar between inhaled and subcutaneously injected insulin ($t = \text{baseline}$, $P = 0.12$). At the end of dosing ($t = 0$ min), serum insulin levels were higher for inhalation treatments than for subcutaneously injected treatments ($P < 0.001$), indicating rapid, systemic insulin absorption following inhalation. The AUC (AUC_{0-8h}) and maximum serum insulin concentration (C_{max} , Table 1) demonstrated a clear dose-response relationship for the three doses of inhaled insulin and the three doses of subcutaneously injected insulin (Fig. 1). Time to maximum insulin concentration (T_{max}) was shorter for inhaled insulin compared with subcutaneously injected insulin at each of the three dose settings (Table 1). In contrast to subcutaneous injection, T_{max} for inhaled insulin was similar across the dose-range studied ($P > 0.05$).

The mean relative bioavailability for inhaled insulin (95% CI) for the low, medium, and high doses was 18% (13–20), 22% (16–25), and 22% (16–24), respectively. There was no significant difference in relative bioavailability for inhaled insulin treatment among the doses, as indicated by overlapping 95% CIs. The higher than expected relative bioavailability re-

sulted in a greater C_{max} and insulin-AUC for inhaled insulin than for subcutaneously injected insulin at each of the three dose levels.

Pharmacodynamics

A dose-dependent increase in AUC for GIR (GIR-AUC) and maximum GIR (GIR_{max}) was observed for both inhaled and subcutaneously injected insulin treatments. At each dose level, GIR_{max} was greater for the inhaled insulin treatment, and T_{GIRmax} was shorter for inhaled insulin than for subcutaneously injected insulin (Fig. 2 and Table 1). There was no effect of dose on T_{GIRmax} for inhaled or subcutaneously injected insulin. The mean relative biopotency for inhaled insulin (95% CI) at the low, medium, and high doses was 13% (11–14), 16% (13–18), and 16% (14–18), respectively. There was no significant difference in relative biopotency for inhaled insulin among the dose studies, as indicated by overlapping 95% CIs.

The dose-response relationships (dose [insulin-AUC $_{0-8h}$] versus response [GIR-AUC $_{0-8h}$]) for inhaled and injected treatments are both shown in Fig. 3. The curves for the two treatments overlapped and, collectively, all data points appeared to lie on a common dose-response curve. Comparison of the slope of inhaled and subcutaneously injected insulin dose-

Table 1—Pharmacokinetic and pharmacodynamic summary measures for inhaled and subcutaneously injected insulin

Parameter	Inhaled insulin			Subcutaneously injected insulin		
	Low (80 units)	Medium (160 units)	High (240 units)	Low (8 units)	Medium (16 units)	High (240 units)
<i>n</i>	16	16	16	16	16	16
Insulin						
AUC _{0–1 h} (mU · ml ⁻¹ · min ⁻¹)*	1.8 ± 1.5	3.2 ± 1.5	5.1 ± 3.0	0.3 ± 0.2	0.6 ± 0.3	0.8 ± 0.2
AUC _{0–3 h} (mU · ml ⁻¹ · min ⁻¹)*	4.9 ± 3.0	10.3 ± 4.2	16.7 ± 8.1	1.8 ± 0.7	3.3 ± 1.1	4.4 ± 1.3
AUC _{0–8 h} (mU · ml ⁻¹ · min ⁻¹)*	7.6 ± 4.5	17.1 ± 6.2	26.8 ± 11.3	4.5 ± 2.6	8.1 ± 2.3	12.6 ± 2.6
AUC _{0–∞} (mU · ml ⁻¹ · min ⁻¹)*	8.0 ± 4.8	20.3 ± 7.0	30.6 ± 12.0	6.6 ± 6.4	8.7 ± 1.9	16.6 ± 5.2
C _{max} (μU/ml)*	44.7 ± 29.1	83.4 ± 36.2	137 ± 68.1	17.6 ± 9.2	29.0 ± 10.2	41.2 ± 11.8
Early t _{50%} (min)*	17.0 ± 21.3	14.8 ± 16.3	14.9 ± 12.6	40.5 ± 28.7	42.7 ± 28.8	42.6 ± 18.3
T _{max} (min)*	60.3 ± 28.3	97.0 ± 106	73.8 ± 28.0	168 ± 109	173 ± 93.9	237 ± 101
GIR						
AUC _{0–1 h} (mg/kg)*	57.5 ± 24.8	88.1 ± 37.2	118.0 ± 79.5	27.7 ± 17.9	28.9 ± 15.5	31.7 ± 15.8
AUC _{0–3 h} (mg/kg)*	369 ± 88.9	567 ± 172	747 ± 314	198 ± 71.8	245 ± 89.2	277 ± 83.3
AUC _{0–8 h} (mg/kg)*	1,085 ± 234	1,737 ± 411	2,440 ± 853	867 ± 204	1,137 ± 317	1,487 ± 425
GIR _{max} (mg · kg ⁻¹ · min ⁻¹)*	3.4 ± 0.9	5.4 ± 1.5	7.2 ± 1.8	2.9 ± 0.7	3.9 ± 1.2	5.2 ± 1.6
Early t _{50%} (min)*	50.7 ± 24.3	53.9 ± 17.0	68.5 ± 26.6	105 ± 59.7	131 ± 65.0	154 ± 52.6
T _{GIRmax} (min)*	225 ± 96.7	223 ± 88.2	274 ± 92.9	366 ± 53.9	347 ± 68.4	349 ± 57.8
Late t _{50%} (min)	456 ± 31.7	440 ± 63.0	460 ± 60.4	472 ± 30.0	470 ± 26.8	470 ± 29.7

Data are means ± SD. *Significant treatment effect ($P < 0.0001$), determined using an ANOVA model including period, treatment, sequence, and subject nested within sequence factors. AUC and C_{max} values were log transformed before analysis.

response curves showed no significant differences between the two treatment groups ($P = 0.62$).

Safety

Examination of group data showed no clinically significant changes in FEV₁ and FVC at 1 and 6 h postdosing compared with baseline ($t = -30$ min). A small

(<3%) but statistically significant decrease from baseline was observed in FEV₁ for the medium and high inhaled insulin group at 6 h postdosing compared with baseline, but this finding was not regarded as clinically relevant. Examination of within-patient changes revealed a single clinically relevant decrease from baseline in FEV₁ (11%) observed in a single

patient at 6 h after subcutaneous injection dosing. A significant FVC change from baseline was observed for the medium inhaled insulin dose group at 1 and 6 h postdosing. This change in the group data was also not regarded as clinically significant (<4%). The clinically significant change in FEV₁ from baseline observed at 6 h postdosing in the patient described above was accompanied by a corresponding decrease (11%) in FVC.

All adverse events recorded during the study were considered mild to moderate in nature. No clinically relevant changes in vital signs, physical examinations, or clinical laboratory values were observed during the study.

CONCLUSIONS— In this first report of a head-to-head dose-response comparison between inhaled and subcutaneously injected insulin treatments, increasing doses of inhaled insulin delivered by the Aerodose insulin inhaler resulted in a dose-dependent increase in serum insulin concentration and a corresponding glucose lowering effect that were similar in proportion to that obtained for increasing doses of subcutaneously injected insulin. Thus, a plot of insulin-AUC versus GIR-AUC showed a dose response for inhaled and subcutaneously injected insulin that overlapped;

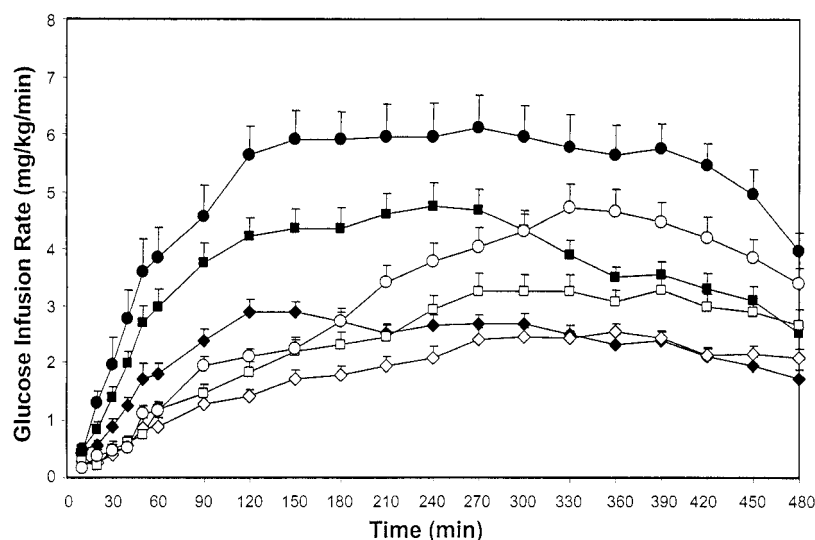


Figure 2—GIR registered following administration of inhaled insulin (◆, 80 units; ■, 160 units; ●, 240 units) and subcutaneous injection (◇, 8 units; □, 16 units; ○, 24 units) in patients with type 2 diabetes. GIRs have been averaged over 30-min periods. Data points are means ± SE ($n = 16$) at each time point for low, medium, and high doses for inhaled and injected insulin.

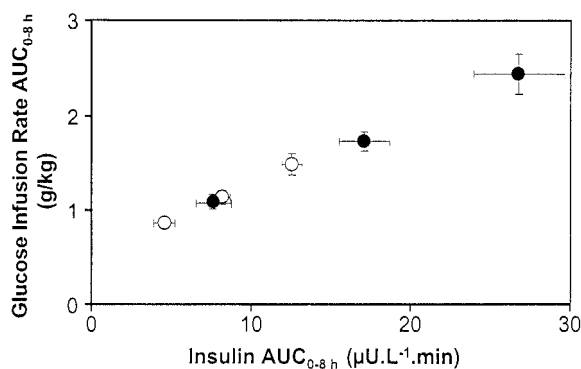


Figure 3—Dose-response (mean insulin-AUC_{0-8 h} versus mean GIR-AUC_{0-8 h}) relationships for inhaled (●) and subcutaneously injected (○) insulin in patients with type 2 diabetes. Data points are means ± SE (n = 16) at each time point for low, medium, and high doses for inhaled and injected insulin.

collectively, the data points from both treatments appeared to fit on a common dose-response curve (Fig. 3). Therefore, the present data indicate that in the dose range studied, the overall glucose lowering effect of increasing doses of insulin is indistinguishable whether insulin is delivered via the subcutaneous or inhaled route. The similar dose response for inhalation and subcutaneous injection was reflected in a consistent relative bioavailability and relative biopotency across the doses tested; a finding that indicates a consistent injection-to-inhalation conversion ratio across the dose range studied. From a clinical perspective, a comparable dose-response indicates that dose adjustments for inhaled insulin will be as pharmacologically predictable as that observed for subcutaneously injected insulin.

In the only previously published dose-response relationship for inhaled insulin, also under a glucose clamp setting, Brunner et al. (2) showed a linear dose-response relationship that was derived from four doses of a liquid insulin preparation delivered via the AERx insulin diabetes management system in patients with type 1 diabetes. However, only a single subcutaneously injected dose was administered in this study, and therefore a direct comparison of injected and inhaled dose-response curves was not possible.

The relative bioavailability and biopotency values observed in this study are at the upper end of the range (5–30%) published by others for inhaled insulin (1,2,8,9). Our attempt to match the inhaled doses delivered to the systemic circulation with that of the injected doses at the three dose levels was based on a 10% relative bioavailability obtained in previous studies in healthy subjects (4,5). However, the 18–22% bioavailability ob-

served in this study of patients with type 2 diabetes resulted from an approximate twofold greater absorption of inhaled insulin than was anticipated. This resulted in a dose response for inhaled insulin that was shifted to a higher dose range than that of subcutaneously injected insulin. A relative bioavailability of 16% recently reported by us (6) using the Aerodose inhaler in patients with type 2 diabetes could not be factored into the matching of the inhaled and injected doses as both studies were performed concurrently.

The mean relative bioavailability and biopotency values reported in this study were also higher than those previously observed by us (6) in this patient population. However, the interpatient variability in bioavailability and biopotency observed in the two studies suggests that there are no meaningful differences in these parameters.

The greater relative bioavailability compared with biopotency observed at each dose level was the result of the greater insulin-AUC values achieved for inhaled versus injected insulin. The dose-response curve for insulin is curvilinear, such that at higher doses increasing levels of insulin result in proportionately smaller increases in the blood glucose-lowering effect of insulin (10,11). The lower biopotency value is, therefore, the result of a proportionally lower GIR-AUC obtained at the greater insulin-AUC for inhaled insulin.

As reported previously by us and others (10,12–16), an earlier time to maximum serum insulin (T_{max}) and physiologic effect (T_{GIRmax}) was observed for inhaled compared with injected treatments. A more rapid rate of insulin absorption across a thin alveolar epithelium-endothelium barrier for inhaled insulin is the most probable explanation for this

difference (17). In this connection it must be mentioned that when U500 regular insulin is given subcutaneously, it has a time-action profile that is right shifted compared with U100 regular insulin given subcutaneously. In this study, however, inhaled U500 regular insulin was absorbed much more rapidly than injected U100 regular insulin. From a therapeutic standpoint, this feature of inhalation treatment should allow for insulin dosing closer to the start of a meal (like that for lispro or aspart insulin) and shorten or possibly eliminate the waiting period between insulin dosing and mealtime that is suggested for injection of regular insulin. Additionally, the finding that T_{max} for inhaled insulin appears to be independent of the administered dose suggests that in the clinical setting, inhaled insulin may have a distinct advantage over subcutaneously injected insulin; the latter shows a significant increase in T_{max} with dose. Whether inhalation treatment will allow for a better coverage of prandial insulin requirements in patients with diabetes will require further investigation.

Inhalation treatment was well tolerated in this study. There was a small (<4%) but statistically significant decrease in FEV₁ and FVC from baseline observed in the medium- and high (FEV₁ only)-dose inhaled insulin groups. In this regard, in a previous study (6) of the same insulin formulations, inhaler, and patient population, a small (5–6%) but statistically significant increase in FEV₁ and FVC from baseline was observed following both inhalation and injection treatments. Due to the relatively small number of subjects in these studies, it is not possible to determine the clinical significance of these changes in pulmonary function. A full assessment of the long-term safety of inhaled insulin can only be determined from long-term studies, which are currently in progress. Additionally, because the bioavailability of inhaled insulin in this study was 18–22%, as compared with 10% in earlier studies with this device in nondiabetic volunteers and 16% in another study of patients with type 2 diabetes (4–6), further studies with a larger number of subjects will need to be conducted to more clearly determine the bioavailability of different doses of inhaled insulin delivered with this device.

In conclusion, a consistent relative bioavailability and biopotency for inhaled insulin treatment across the dose range

and an overlapping dose-response curve with that of subcutaneously injected insulin indicates that the Aerodose insulin inhaler delivers insulin with a pharmacological predictability similar to that of subcutaneous injection in patients with type 2 diabetes.

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