Dose Response of Inhaled Dry-Powder Insulin and Dose Equivalence to Subcutaneous Insulin Lispro

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OBJECTIVE — To determine the pharmacokinetic (PK) and glucodynamic (GD) dose response of human insulin inhalation powder (HIIP) delivered via AIR particle technology and dose equivalence to subcutaneous (SC) insulin lispro.

RESEARCH DESIGN AND METHODS — Twenty healthy, nonsmoking, male or female subjects (aged 29.6 ± 6.9 years, BMI 23.2 ± 2.3 kg/m^2, means ± SD) with normal forced vital capacity and forced expiratory volume were enrolled in an open-label, randomized, seven-period, euglycemic glucose clamp, cross-over trial. Each subject received up to four single doses of HIIP (2.6, 3.6, 5.2, or 7.8 mg) and three doses of SC lispro (6, 12, or 18 units) from 5 to 18 days apart.

RESULTS — HIIP demonstrated a similar rapid onset but an extended time exposure and a prolonged duration of effect (late $t_{50\%}$ 412 vs. 236 min, $P < 0.001$) compared with SC lispro. The HIIP versus SC lispro doses of 2.6 mg vs. 6 units, 5.2 mg vs. 12 units, and 7.8 mg vs. 18 units achieved similar PK area under the serum immunoreactive insulin (IRI) concentration-versus-time curve from time zero until the serum IRI concentrations returned to the predose baseline value [$AUC_{(0-t')}$] and GD (G_{tot}) responses. The median insulin (t_{max}) was not different between HIIP and SC lispro (45 min for both), although the median time of return to baseline for PK was apparently longer for HIIP compared with SC lispro (480 vs. 360 min). Relative bioavailability and relative biopotency of HIIP were consistent across doses (8 and 9%).

CONCLUSIONS — While the time-action profile was longer for HIIP than for SC lispro, both treatments showed rapid initial absorption and similar overall PK exposure and GD effect. HIIP was as well tolerated as SC lispro, thereby offering a promising alternative to injectable insulin therapy.

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The disease burden of diabetes continues to grow and currently affects >18 million Americans and their families (1). Despite increased use of diabetes medications (without, however, increased utilization of insulin), overall diabetes control A1C among individuals diagnosed with diabetes in the U.S. has not improved, with A1C rising from 7.7 to 7.9% during the final decade of the last century (2). These data emphasize a need for alternative diabetes therapies with earlier more physiologic use of insulin.

The delivery of insulin by the lung may provide an attractive alternative for many patients with diabetes (3–8). However, alternative insulin delivery systems must meet certain pharmacokinetic (PK) and glucodynamic (GD) requirements to reach maximum utility (9). Specifically, the dose-response characteristics of inhaled insulin should be similar to those of injectable insulins, like human regular insulin or fast-acting insulin analogs such as insulin lispro. Moreover, inhaled insulin should demonstrate satisfactory dose reproducibility; that is, intrasubject variability of inhaled insulin should be similar to or better than that of injectable insulin. Finally, the ratio of dose equivalence between inhaled insulin and injectable insulin ought to be consistent across a range of doses. The present study evaluated the key performance features of a novel inhaled insulin delivery system based on AIR particle technology (10–12) (Alkermes, Cambridge, MA) (including time exposure and time-action profiles, PK and GD dose-response relationships, dose reproducibility, relative bioavailability, and relative biopotency compared with subcutaneous [SC] insulin lispro).

RESEARCH DESIGN AND METHODS

Twenty-two healthy, nonsmoking, male (10) or female (12) subjects with normal pulmonary function (at least 75% of predicted forced expiratory volume [FEV$_1$] and forced vital capacity [FVC]) participated in the study. The age of the subjects was (means ± SD) 29.6 ± 6.9 years, and BMI was 23.2 ± 2.3 kg/m^2. Subjects were ineligible if they had a history of asthma or a recent upper respiratory infection or if they had a medical history of diabetes, impaired glucose tolerance, allergy to insulin, or a fasting blood glucose >5.6 mmol/l. Pregnant women, nursing mothers, and subjects with serious medical conditions were also excluded. The local ethics committee approved the protocol. This phase I clinical trial was conducted according to the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Guideline to Good Clinical Practice. All subjects were given a full explanation of study procedures at the screening visit, and a signed informed consent was obtained for every subject.

This open-label, randomized, seven-period, incomplete block, cross-over, euglycemic glucose clamp study was conducted at one center (Profil Institut

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für Stoffwechselforschung, Neuss, Germany). Each subject received up to four single doses of human insulin inhalation powder (HIIP) (Eli Lilly and Company, Indianapolis, IN) (2.6, 3.6, 5.2, and 7.8 mg) and three single doses of SC lispro (Humalog; Eli Lilly and Company) supplied in 10-ml vials (100 units/ml; 6, 12, or 18 units), ~5–18 days apart. The order of doses was randomized in accordance with an incomplete block study design, where one-third of the subjects received all seven of the possible treatment conditions specified above and two-thirds of the subjects received five of these treatments, with two treatments being performed in replicate. Two different formulations of HIIP were used in this study. The first formulation comprised the 2.6-, 5.2-, and 7.8-mg dose, while the secondary HIIP formulation was represented by the 3.6-mg dose. The latter was administered to determine bioequivalence to the 2.6-mg primary formulation dose. Because the focus of this report is dose response and dose equivalence compared with SC insulin lispro of the HIIP primary formulation, data for the 3.6-mg dose are not presented here.

There was a total of nine visits, including an initial screening visit and a final visit for a medical examination. At each visit in which a glucose clamp procedure was performed (visits 2–8), insulin was administered by inhalation or SC lispro injection ~90 min after the start of the baseline glucose clamp procedure. The investigative staff trained each subject on the proper inhalation technique before pulmonary administration. Subjects were trained to inhale at ~30 l/min for the duration of 5 s using a real-time recording spirometer attached to the inhaler device.

System description
The inhaled insulin system used in this study included a developmental version of the inhaler (Fig. 1) and AIR particle technology (10–12) (Alkermes) to deliver HIIP to the lung. The AIR powder is formulated in capsules that are punctured before inhalation. Each individual particle contains both drug and excipient within a large, low-density matrix (10, 11). HIIP formulated in this manner has low cohesive forces but retains small effective aerodynamic diameter and can thus be aerosolized and delivered to the deep lung using a simple breath-actuated inhaler (12).

Figure 1—*Breath-actuated inhaler.*

Safety measurements
Routine physical examinations and electrocardiograms were performed at screening and at visit 9 (or early termination from the study). Flow-volume spirometry (FEV_1 and FVC) was performed at screening and at visit 9 to assess safety. For visits that included HIIP dosing, FEV_1 and FVC were measured using a portable spirometer within 90 min before dosing and within 60 min after the end of the glucose clamp procedure.

PK analyses
Serum immunoreactive insulin (IRI) concentrations following administration of HIIP and SC lispro (Humalog) were measured using a conventional, competitive radioimmunoassay method validated over the range of 20–2,500 pmol/l (MDS Pharma Services, St. Laurent QC, Canada). The antibody used had comparable cross-reactivity with both native human insulin and insulin lispro and thereby provided relevant IRI concentrations for each treatment.

Noncompartmental PK parameters, computed using WinNonlin (Professional edition, version 3.1; Pharsight, Cary, NC), included the maximum serum IRI concentration (C_{max}), the time of maximum serum IRI concentration (t_{max}), and the area under the serum IRI concentration-versus-time curve from time zero until the serum IRI concentrations returned to the predose baseline value [$AUC_{(0-t')}$]. An assessment of relative bioavailability (F) for HIIP compared with SC lispro was conducted based on $AUC_{(0-t')}$ according to equation 1:

$$F = \frac{D_{SC} \cdot AUC_{(0-t')HIIP}}{D_{HIIP} \cdot AUC_{(0-t')SC}} \quad (1)$$

where D is dose and $AUC_{(0-t')}$ is the IRI AUC from zero to return to baseline for HIIP and SC lispro treatments.

The SAS system for Windows (version 8.2) was used for the statistical analyses of both PK and GD parameters. The primary analysis variable $AUC_{(0-t')}$, secondary variable, C_{max}, and the dose (milligrams) were log transformed before statistical analysis. The dose-response relationship was described separately for HIIP and SC lispro using a mixed-effects ANCOVA with fixed factors for sequence, log (dose) used as a covariate and subject as a random factor, and was performed separately for HIIP and SC lispro. No direct comparisons of $AUC_{(0-t')}$ or C_{max} were made between HIIP and SC lispro. Rather, the HIIP dose expected to yield the same PK response as the corresponding SC lispro dose was estimated by back calculation from the ANCOVA results. The 95% CIs for the predicted HIIP doses were constructed based on Fieller's theorem (13) and incorporated variance estimates from both HIIP and SC lispro ANCOVA analyses.

GD analyses
The euglycemic glucose clamp procedure was used to measure the effect of HIIP or SC lispro treatments. Baseline blood glucose concentrations were obtained before exogenous insulin administration. The glucose clamp procedure was designed to maintain blood glucose at a level ~5% below baseline for up to 10 h after insulin administration (14). Blood glucose concentrations were monitored on a minute-to-minute basis by the Biostator (glucose-controlled insulin infusion system; Medizintechnik, Ulm, Germany), which automatically adjusted a 20% intravenous glucose infusion to maintain euglycemia.

Table 1—*PK and GD results following administration of HIIP or SC insulin lispro*

	HIIP			SC lispro		
	2.6 mg	5.2 mg	7.8 mg	6 units	12 units	18 units
PK parameters						
PK predicted HIIP dose (mg) (95% CI)	3.4 (2.6–4.4)	5.3 (4.3–6.6)	6.9 (5.5–9.0)	—	—	—
$AUC_{(0-t')}$ (pmol · min^{-1} · l^{-1})	28,500 (42.8)	59,000 (51.1)	105,000 (46.8)	37,100 (25.2)	65,800 (33.2)	78,700 (39.3)
C_{max} (pmol/l)	161 (50.3)	287 (58.3)	512 (60.1)	311 (22.4)	414 (34.6)	523 (43.3)
N_{PK}	12	31	13	8	32	12
t_{max} (min)	45 (10–120)	30 (10–120)	45 (20–120)	45 (30–90)	45 (20–180)	45 (30–90)
Percent F	7.35 (62.8)	7.39 (61.9)	8.90 (58.5)	—	—	—
GD parameters						
GD predicted HIIP dose (mg) (95% CI)	2.6 (1.8–3.6)	5.0 (3.8–6.7)	7.4 (5.6–10.5)	—	—	—
G_{tot} (0–600) (mg)	87,200 (48.5)	137,000 (37.1)	175,000 (40.6)	82,500 (42.4)	132,000 (35.3)	161,000 (29.8)
R_{max} (mg/min)*	267 (55.7)	425 (38.1)	499 (34.1)	423 (44.3)	563 (37.8)	672 (34.6)
N_{GD}	12	31	13	12	32	14
t_{Rmax} (min)*†	260 (44–489)	191 (65–315)	211 (66–374)	85 (63–188)	112 (64–211)	136 (84–211)
t_{onset} (min)‡	13 (20–31)	13 (2–34)	15 (4–27)	24 (2–29)	16 (4–33)	22 (7–41)
Early $t_{50\%}$ (min)*§	40 (10–185)	43 (21–139)	33 (16–139)	35 (25–55)	38 (15–53)	38 (27–61)
Late $t_{50\%}$ (min)*‖	458 (252–575)	371 (242–568)	404 (280–592)	184 (125–308)	248 (158–326)	273 (199–360)
Percent F′	9.74 (52.1)	8.28 (47.4)	8.32 (43.0)	—	—	—

Data are geometric mean (% CV) and median (range) unless otherwise indicated. *Observed from Loess smoothed data; †$P < 0.001$ for HIIP vs. SC lispro; ‡$P = 0.005$ for HIIP vs. SC lispro; §$P = 0.013$ for HIIP vs. SC lispro; ‖$P < 0.001$ for HIIP vs. SC lispro. F, relative bioavailability; F′, relative biopotency.

A LOESS smoothing function was fitted to the glucose infusion rate (GIR) data by means of S-plus (version 2000). The maximum GIR (R_{max}) and the time of maximum GIR (t_{Rmax}) were identified from the individual LOESS-fitted data. Other parameters, such as the times of 50% of maximum GIR before and after R_{max} (early and late $t_{50\%}$), were also calculated based on the individual LOESS-fitted data. The total amount of glucose infused from time 0 to 10 h (G_{tot}) and the time of the first change in the GIR (t_{onset}) were calculated from the raw GIR data. An additional LOESS fit was performed, where all GIR data from all subjects were fitted simultaneously in order to obtain predicted values per dose group. The relative biopotency (F′) of HIIP compared with SC insulin lispro was calculated based on G_{tot}, according to equation 2:

$$F' = \frac{D_{SC} \cdot G_{tot_{HIIP}}}{D_{HIIP} \cdot G_{tot_{SC}}} \quad (2)$$

where D is dose and G_{tot} is the total amount of glucose infused from time 0 to 10 h for HIIP and SC insulin lispro treatments.

The primary analysis variable G_{tot}, the secondary variable R_{max}, and the dose (milligrams) were log transformed before statistical analysis. A mixed-effects AN-COVA was performed as described for the PK measures to determine the dose-response relationship for both HIIP and SC insulin lispro. The GD time variables were directly compared between HIIP and SC insulin lispro using a mixed-effect ANOVA with fixed factors for insulin, dose, and sequence and a random factor for subject.

RESULTS

Subject disposition

Twenty of 22 subjects who entered the study proceeded to the first euglycemic clamp visit and received a study drug on at least one occasion. Eighteen subjects completed all study visits. None of the subjects discontinued due to an adverse event. Safety data from all 22 subjects were included in the safety analyses. Subjects who completed at least one glucose clamp procedure were included in the GD analyses. Those who completed one glucose clamp and had measurable IRI concentrations were included in the PK analyses. All available PK and GD data were included in the statistical analyses.
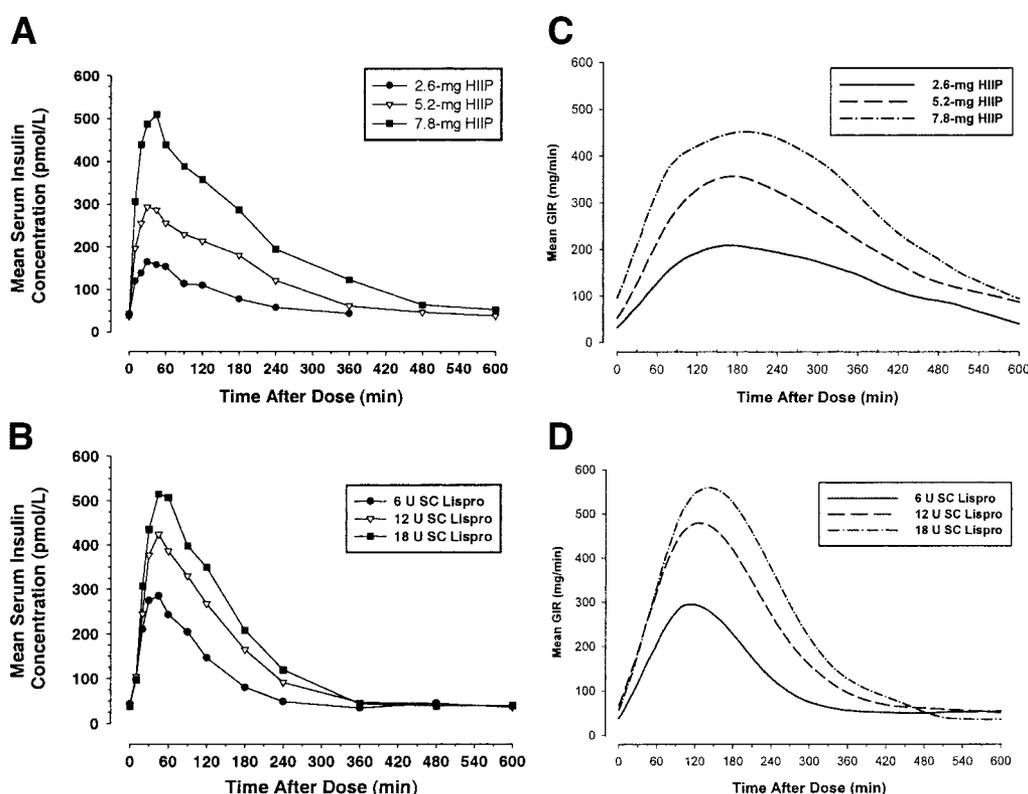
PK and GD results

A positive trend in the exposure versus time and the effect versus time profiles confirmed the PK and GD dose-response relationships for HIIP (Fig. 2). In its early PK profile, HIIP demonstrated a rapid initial absorption comparable with that of SC lispro (Fig. 2A and B). The rapid initial absorption of HIIP was reflected in its GD profile, that is, a slightly but significantly earlier onset of action compared with SC lispro ($P = 0.005$). Following this accelerated onset, HIIP demonstrated a prolonged insulin time-concentration profile that was correlated with a longer duration of effect compared with SC lispro (Table 1).

For doses of HIIP comparable with SC lispro (2.6 mg to 6 units, 5.2 mg to 12 units, and 7.8 mg to 18 units, respectively), mean $AUC_{(0-t')}$ values were similar, while mean C_{max} values appeared to be lower for HIIP. Thus, even though the insulin concentration versus time profile appeared to be prolonged for HIIP compared with SC lispro, the total insulin exposure was comparable for corresponding doses. Both the PK and GD profiles were flatter for HIIP than for SC lispro (Fig. 2A–D), and at doses that provided similar overall exposure, total GD effects were also comparable (Table 1).

Based on $AUC_{(0-t')}$, intersubject variability appeared to be larger for HIIP (42%) than for SC lispro (15%), while intrasubject variability was comparable between both (30%). Based on G_{tot}, intersubject variability was comparable

Figure 2—*PK and GD results after inhalation of HIIP and SC lispro injection. A: Mean serum insulin concentration versus time profiles of three different doses of HIIP. B: Mean serum insulin concentration versus time profiles of three different doses of SC lispro. C: Plots of simultaneous LOESS fits of GIR versus time data of three different doses of HIIP. D: Plots of simultaneous LOESS fits of GIR versus time data of three different doses of SC lispro.*

between HIIP and SC lispro (27%), and intrasubject variability was comparable between both as well (28%). The predicted doses of HIIP that would be interchangeable with 6, 12, and 18 units of SC lispro were in excellent agreement with inhalation of the 2.6-, 5.2-, or 7.8-mg doses of HIIP (Table 1). The overall mean relative bioavailability and relative biopotency of HIIP compared with SC lispro across all doses tested were ~8 and 9%, respectively.

Safety
Review of the laboratory, vital signs, electrocardiogram, and pulmonary function data revealed no safety findings of clinical relevance. The postdose mean FVC increased in magnitude compared with the predose FVC; however, the increase was slight and was not considered clinically significant (predose means ± SE: 110.7 ± 2.5% of predicted value; postdose means ± SE: 113.3 ± 2.5%; $P = 0.003$). For FEV_1, there was no statistically significant difference between the predose and postdose mean values ($P = 0.134$). A single adverse event was reported that entailed a case of mild, non-

serious influenza but was not considered by the investigator to be study related.

CONCLUSIONS — This open-label, cross-over study in healthy subjects showed that inhalation of the HIIP formulation was safe and produced a similar initial rate of absorption, an extended insulin exposure, and a prolonged duration of effect when compared with SC lispro PK and GD profiles. Although C_{max} values appeared to be lower with HIIP, the overall exposure and metabolic effect at similar doses was comparable between HIIP and SC lispro, as evidenced by both the PK and GD profiles being flatter for HIIP. This observation of comparable overall exposure and metabolic effect, coupled with the comparable intrasubject variability estimates for HIIP and SC lispro, suggests that patients may be able to transition between inhaled and SC lispro treatment with predictable results.

In a clinical setting, predictable dose equivalence is important for successfully switching patients between different insulin formulations and routes of administration. This is the first study investigating dose equivalence of inhaled insulin versus

an SC injected rapid-acting insulin analog like insulin lispro. With this study, we were able to demonstrate that the predicted doses were in good agreement with the actual HIIP doses used in the study, as confirmed by the narrow 95% CI observed for the predicted doses.

The safety and tolerability of all HIIP doses was assessed as excellent, as no pulmonary-related adverse events were reported. This aligns with other studies using different insulin delivery systems in healthy subjects (15–17) and patients with type 1 (18,19) and type 2 (20–22) diabetes, during which pulmonary function testing was performed using spirometry. However, when measuring carbon monoxide lung diffusing capacity (DL_{co}) small decreases were noted following inhalation of dry-powder insulin in several phase 2 and 3 studies of Exubera (18,22,23). The decreases in DL_{co} occur quickly, are not progressive, and have not been associated with any clinical manifestations to date (18,22,23). As the current study focused on dose response and dose equivalence of HIIP in comparison to SC insulin lispro, DL_{co} was not measured, which represents a limitation of the study.

The most common respiratory adverse event in studies of inhaled Exubera is mild-to-moderate cough following inhalation of dry-powder insulin (18,22,23). The incidence of cough decreases over time and has not been associated with declines in lung function (18). It is remarkable that in the current study not a single episode of cough was registered, suggesting an excellent tolerability of the inhaled insulin when formulated by the AIR particle technology. This result, however, needs to be confirmed in much larger phase 3 trials.

The administration of HIIP by means of a simple, handheld, breath-actuated inhaler in healthy subjects in this glucose-clamp study exhibited a slightly more rapid initial absorption of insulin compared with SC lispro coupled with a longer duration of metabolic activity than seen with SC lispro. These findings agree with other studies (24,25) comparing inhaled insulin with SC insulin lispro. In addition, the intrasubject variability for overall insulin exposure and GD effect was comparable with SC lispro. This finding also agrees with previous studies (21,26,27) investigating a number of different technologies for the delivery of inhaled insulin. One inhaled insulin system that demonstrates a different PK and GD profile is that of Technosphere (MannKind, Valencia, CA). This formulation exhibits a very rapid onset and very short (3 h) duration of insulin exposure and action when compared with regular SC insulin (16,28,29).

Taken together, these results support the potential utility of inhaled insulin as an alternative to insulin injections. Because the fear of injections is a frequent cause for delaying appropriate care in patients with type 2 diabetes, inhaled insulin may provide a treatment that delivers effective doses of insulin in a less threatening, more satisfying manner, potentially resulting in improved patient compliance and better outcomes.

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