Time-Action Profile of Inhaled Insulin in Comparison With Subcutaneously Injected Insulin Lispro and Regular Human Insulin

Klaus Rave, MD[1]
Susanne Bott, MD[1]
Lutz Heinemann, PHD[1]
Sue Sha, MD, PHD[2]
Reinhard H.A. Becker, MD, PHD[3]
Susan A. Willavize, PHD[2]
Tim Heise, MD[1]

OBJECTIVE — This study compares the time-action profile of inhaled insulin (INH; Exubera) with that of subcutaneously injected insulin lispro (ILP) or regular human insulin (RHI) in healthy volunteers.

RESEARCH DESIGN AND METHODS — In this open-label, randomized, three-way, crossover study, 17 healthy male volunteers were given each of the following treatments in random order: INH (6 mg), ILP (18 units), or RHI (18 units). Glucose infusion rates and serum insulin concentrations were monitored over 10 h.

RESULTS — INH had a faster onset of action than both RHI and ILP, as indicated by shorter time to early half-maximal effect (32 vs. 48 and 41 min, respectively; $P < 0.001$ for IHN vs. RHI and $P < 0.05$ for IHN vs. ILP). Time to maximal effect was comparable between INH and ILP (143 vs. 137 min; NS) but was shorter for INH than RHI (193 min; $P < 0.01$). The maximal metabolic effect of INH was comparable with RHI but lower than ILP (8.7 vs. 9.8 vs. 11.2 mg · kg^{-1} · min^{-1}, respectively; $P < 0.01$ for INH vs. ILP). The duration of action of INH, indicated by time to late half-maximal effect (387 min), was longer than ILP (313 min; $P < 0.01$) and comparable to RHI (415 min; NS). Total glucodynamic effect after inhalation of INH was comparable to both ILP and RHI (NS). Relative bioefficacy of INH was 10% versus RHI and 11% versus ILP. No drug-related adverse events were observed.

CONCLUSIONS — INH had a faster onset of action than RHI or ILP and a duration of action longer than ILP and comparable to RHI. These characteristics suggest that inhaled insulin is suitable for prandial insulin supplementation in patients with diabetes.

Diabetes Care 28:1077–1082, 2005

The pulmonary delivery of insulin is currently being studied as an alternative method of insulin administration. Early studies have shown promising results, and it has been demonstrated that the onset of action of inhaled insulin is faster than that of regular human insulin (RHI), resembling that of rapid-acting insulin analogs (1–5). RHI has several disadvantages when its use for controlling prandial glycemia is considered. A relatively slow onset of action and a prolonged duration of action results in a suboptimal time-action profile (6). In addition, subcutaneous insulin injections are often considered inconvenient and cause anxiety for many patients (7).

Inhaled insulin may be a viable alternative to prandial insulin administration for patients with diabetes because of its more favorable pharmacokinetic profile and less invasive route of administration. However, a direct comparison of the pharmacodynamic properties of INH and subcutaneously injected rapid-acting insulin analogs has not yet been performed. The purpose of this study was to compare the pharmacokinetic and pharmacodynamic properties of human insulin administered to the lung using a novel dry-powder inhaled insulin delivery system with those of subcutaneously injected RHI and the rapid-acting insulin analog insulin lispro (ILP).

RESEARCH DESIGN AND METHODS

Eighteen healthy, nonsmoking male volunteers (age 28 ± 4 years, BMI 23.6 ± 2.0 kg/m^2) participated in this open-label, randomized, three-way, crossover study. Seventeen participants completed the study; one withdrew after receiving his first study treatment (INH) due to an adverse event (sepsis) attributed to the testing procedure and not the study treatment.

Subjects gave written informed consent and underwent a physical examination, 12-lead electrocardiogram recording, and clinical laboratory tests. All subjects had normal lung function (mean forced expiratory volume in 1 s [FEV_1] >80% of predicted normal value; FEV_1–to–forced vital capacity ratio >0.80) as measured in a standing position using a Spirovit SP-200 (Schiller AG, Baar, Switzerland). Nonsmoking status was verified using a negative urine cotinine excretion test (LCMS method, API 3+; Perkin-Elmer, Weiterstadt, Ger-

From the [1]Profil Institut für Stoffwechselforschung, Neuss, Germany; [2]Pfizer Global Research and Development, Groton, Connecticut; and [3]Aventis Pharma Deutschland, Frankfurt, Germany.
Address correspondence and reprint requests to Tim Heise, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, D-41460 Neuss, Germany. E-mail: tim.heise@profil-research.de.
Received for publication 26 July 2004 and accepted in revised form 19 January 2005.
Abbreviations: AUC, area under the curve; FEV, forced expiratory volume; GIR, glucose infusion rate; ILP, insulin lispro; INH, inhaled insulin; RHI, regular human insulin.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

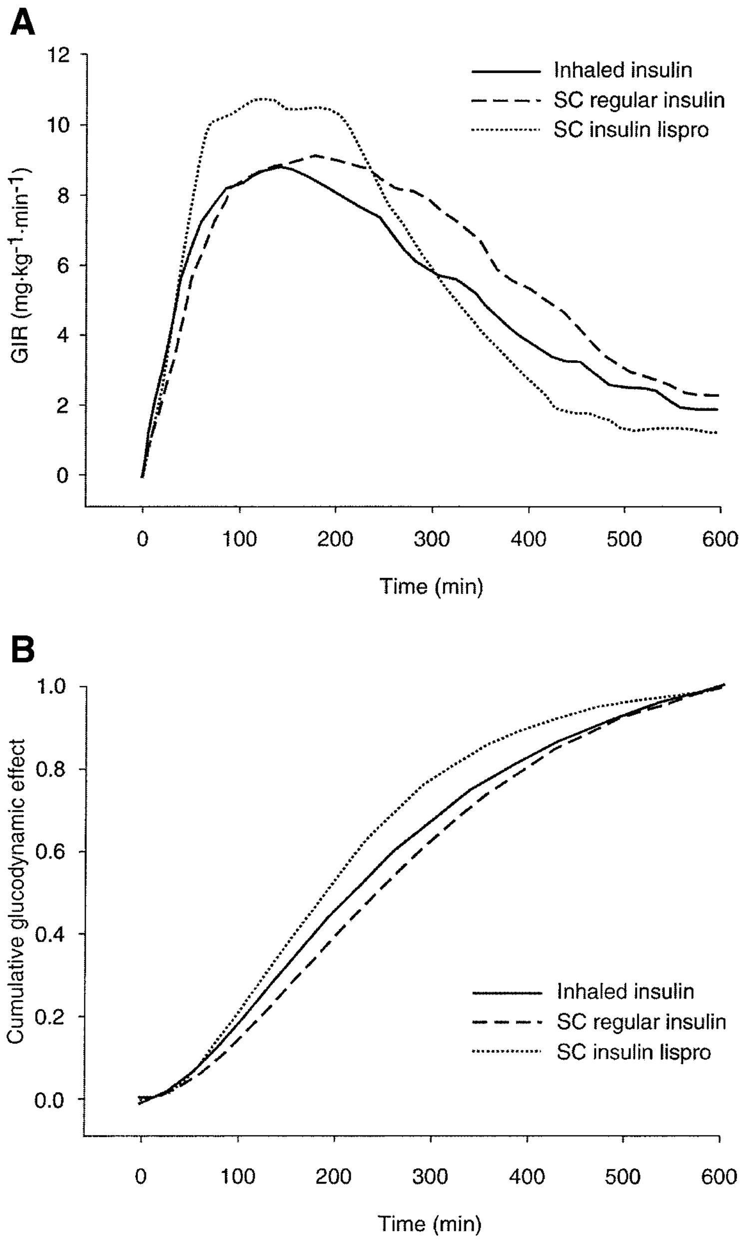

Figure 1 —A: *Baseline-corrected GIRs registered in 17 healthy volunteers after inhalation of 6 mg insulin, subcutaneous injection of 18 units regular insulin, and subcutaneous injection of 18 units insulin lispro (LOESS smoothed data).* B: *Cumulative glucodynamic effect. The relative glucose consumption for each of the insulins from the beginning of the glucose clamp to any time point is expressed as a proportion of the total glucose consumption during the entire clamp period (i.e., AUC-GIR$_{0-600}$).*

many). The study was carried out in accordance with the principles of the Declaration of Helsinki and of good clinical practice and was approved by the local ethics committee.

There were three dosing periods separated by 7–21 days. After an overnight fasting period, subjects were connected to a Biostator (Life Science Instruments, Elkhardt, IN) for glucose infusion to maintain glucose concentrations at a target level (90 mg/dl or 5.0 mmol/l). A basal intravenous insulin infusion (Actrapid U100; Novo Nordisk, Bagsvaerd, Denmark) at 0.15 mU · kg^{-1} · min^{-1} (infusion pump, Midpress TE*171CW3; Terumo, Tokyo, Japan) was applied throughout the study to suppress endogenous insulin secretion and establish comparable serum insulin concentrations before administration of the study medication (~10–15 μU/ml).

After a baseline period of 120 min, subjects received one of the following three treatments in a random order: INH 6 mg (two 3-mg doses; Exubera), ILP 18 units (Humalog; Eli Lilly, Indianapolis, IN), or RHI 18 units (Humulin; Eli Lilly) at time point zero. ILP and RHI were administered by subcutaneous injection using disposable insulin syringes (low-dose microfine IV+, 0.3 ml; Becton Dickinson, Heidelberg, Germany) into a lifted skinfold in the abdomen. INH was administered as an aerosolized cloud from the holding chamber (240 ml) of the mechanical handheld dry-powder inhaler (Nektar Therapeutics, San Carlos, CA). One milligram of Exubera contains 27.5 units of human insulin, which provides approximately the same total efficacy as 3 units of RHI subcutaneously (8).

Volunteers were instructed to inhale steadily and deeply over 5–10 s after a normal exhalation and to hold their breath for 5 s afterward. Each administration of 6 mg insulin comprised two inhalation procedures, each of 3 mg insulin. The second procedure was performed within 1 min of the first. Glucose infusion rates (GIRs) necessary to keep blood glucose constant at the target level were recorded electronically every minute for 600 min after administration of insulin.

Pharmacokinetic and pharmacodynamic evaluations

Blood samples to determine serum insulin concentrations were collected at −120, −60, −30, −15, 0 min (just before insulin dosing), 5, 10, 20, 30, 40, 50, 60, 75, 90, and 120 min, and then hourly until the end of each clamp procedure (600 min). Blood glucose was measured using the glucose oxidase method (Super GL; Hitado Dellecke-Möhnesee, Germany) to readjust the Biostator glucose measurements in 30 min intervals. Serum insulin concentrations were measured by radioimmunoassay (Phoenix International Life Science, Montreal, QC, Canada) using an insulin antibody with a theoretical 100% cross-reactivity to ILP. However, due to the possibility of <100% crossreactivity, the pharmacokinetic profile of ILP is not reported here.

Statistical methods

A one-sided significance level of 0.05 was used to test the hypothesis that INH and

Table 1—*Mean pharmacodynamic summary measures of 6 mg INH, subcutaneous injection of 18 U RHI, and subcutaneous injection of 18 U ILP on three different study days in 17 healthy volunteers (baseline values subtracted)*

Serum glucose measures	INH (A)	ILP (B)	RHI (C)	Ratio/difference	90% CI	*P* values*
Time to early half-maximal effect ($t_{GIR\ early\ 50\%}$) (min)†	32	41	48	−17 (A−C)	−24 to −10	<0.001
				−10 (A−B)	−17 to −3	<0.05
				−7 (B−C)	−14 to 0	NS
Maximal metabolic effect (GIR_{max}) ($mg \cdot kg^{-1} \cdot min^{-1}$)‡	8.7	11.2	9.8	89% (A/C)	79–101	NS
				78% (A/B)	69–88	<0.01
				115% (B/C)	101–130	NS
Time to maximal effect (t_{GIRmax}) (min) †	143	137	193	−49 (A−C)	−77 to −21	<0.01
				7 (A−B)	−22 to 35	NS
				−56 (B−C)	−84 to −28	<0.01
Time to late half-maximal effect ($t_{GIR\ late\ 50\%}$) (min)†	387	313	415	−29 (A−C)	−71 to 13	NS
				74 (A−B)	32–116	<0.01
				−103 (B−C)	−145 to −61	<0.001
$AUC\text{-}GIR_{0-60}$ (g/kg)‡	0.23	0.24	0.17	134% (A/C)	107–168	<0.05
				96% (A/B)	76–120	NS
				140% (B/C)	112–176	<0.05
$AUC\text{-}GIR_{0-180}$ (g/kg)‡	1.21	1.45	1.17	103% (A/C)	90–119	NS
				84% (A/B)	73–96	<0.05
				124% (B/C)	108–142	<0.05
$AUC\text{-}GIR_{0-600}$ (g/kg)‡	3.03	3.16	3.44	88% (A/C)	77–101	NS
				96% (A/B)	84–110	NS
				92% (B/C)	80–105	NS

*One-sided for t_{GIRmax} and $AUC\text{-}GIR_{0-60}$; two-sided for all other measures; †arithmetic mean; ‡geometric mean.

ILP had greater areas under the curve (AUC) and shorter time to maximal effect (t_{max}) for the GIR and insulin concentration (for INH only) compared with RHI. All other comparisons were analyzed to determine whether the two-sided *P* value was significant at $\alpha < 0.05$.

For each subject and for each treatment day, the GIR was corrected for baseline GIR estimated as the mean of predose GIR values. If corrected postdose GIR values were <0, they were set equal to zero. These baseline corrected GIR values were then smoothed by fitting a sixth-degree polynomial function. The resultant smoothed GIR values were assessed as follows: the maximum GIR (GIR_{max}), time to GIR_{max} (t_{GIRmax}), time to half of GIR_{max} before GIR_{max} ($t_{GIR\ early\ 50\%}$), and time to half of GIR_{max} after GIR_{max} ($t_{GIR\ late\ 50\%}$). The area under the GIR versus time curve (AUC-GIR) was calculated on the baseline corrected raw GIR values by means of the trapezoid rule to summarize the total amount of glucose infused for the intervals of time points 0–60 min ($AUC\text{-}GIR_{0-60}$), 180 min ($AUC\text{-}GIR_{0-180}$), and 600 min ($AUC\text{-}GIR_{0-600}$).

Natural log-transformed GIR and insulin AUCs, GIR_{max} and insulin C_{max} and untransformed t_{GIRmax}, insulin t_{max}, $t_{GIR\ early\ 50\%}$, and $t_{GIR\ late\ 50\%}$ were analyzed using an ANOVA model containing sequence, subject-within-sequence, period, treatment, and treatment-by-period effects. SAS (Cary, NC) procedure GLM (general linear models) was used for these analyses. The LSMEANS statement of SAS was used to estimate the adjusted means and their variances and covariances. These estimates were then used to estimate the adjusted mean difference between treatment effects, their standard errors, and the 90% CIs of the difference. For GIR AUCs, GIR_{max}, and insulin C_{max}, the antilog (exponent) of the differences and confidence limits was taken to estimate the ratio between treatment effects and the 90% CI of the ratio. For t_{GIRmax}, insulin t_{max}, $t_{GIR\ early\ 50\%}$, and $t_{GIR\ late\ 50\%}$, the 90% CI of the mean difference was calculated. Geometric means were provided for GIR and insulin AUCs and GIR_{max} and insulin C_{max}. Arithmetic means were provided for t_{GIRmax}, insulin t_{max}, $t_{GIR\ early\ 50\%}$, and $t_{GIR\ late\ 50\%}$. Relative efficacy was calculated as the ratio of the dose-adjusted GIR AUCs for INH and both subcutaneous insulins: $([dose_{sc}/dose_{INH}] \times [AUC_{INH}/AUC_{sc}]) \times 100$. Relative bioavailability was calculated using insulin AUCs.

RESULTS

Pharmacodynamic results

Baseline glucose consumption was comparable for all three study days. As shown in Fig. 1 and Table 1, the onset of action of INH, as assessed by $t_{GIR\ early\ 50\%}$, was significantly more rapid than that of both RHI (32 vs. 48 min; $P < 0.001$) and ILP (41 min; $P < 0.05$). Time to maximal effect (t_{GIRmax}) was comparable between INH and ILP (143 vs. 137 min; NS) but was shorter for INH compared with RHI (193 min; $P < 0.01$). Maximal metabolic effect (GIR_{max}) for INH or RHI was lower than for ILP (8.7 and 9.8 vs. 11.2 $mg \cdot kg^{-1} \cdot min^{-1}$; $P < 0.01$ and $P = 0.069$, respectively), as also shown in Fig. 1. Duration of metabolic activity ($t_{GIR\ late\ 50\%}$) of INH (387 min) was longer than that of ILP (313 min; $P < 0.01$) and comparable to that of RHI (415 min, NS).

The rapid onset of action of INH was also reflected in the higher glucose consumption during the first hour after administration ($AUC\text{-}GIR_{0-60}$) compared with RHI (0.23 vs. 0.17 g/kg; $P < 0.05$).

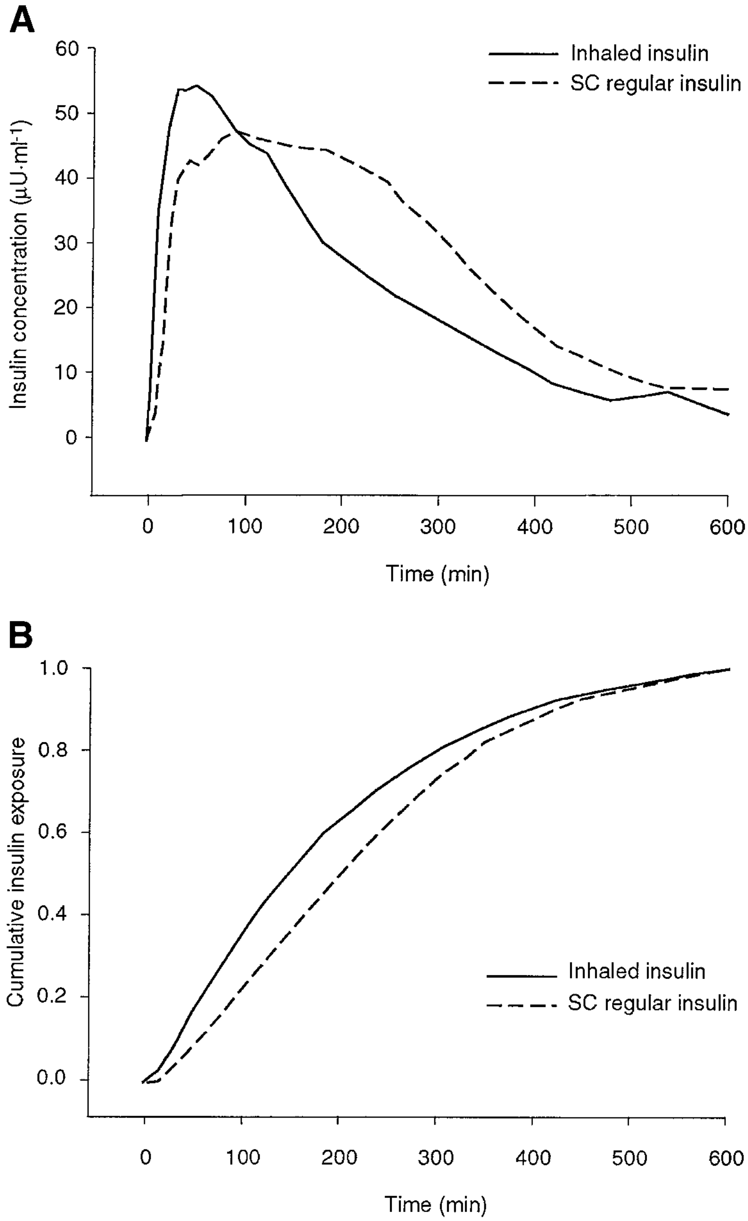

Figure 2 —A: *Baseline-corrected serum insulin concentration time profile assayed in 17 healthy volunteers after inhalation of 6 mg insulin or subcutaneous injection of 18 units regular insulin (LOESS smoothed data).* B: *Cumulative insulin exposure. The relative insulin exposure for each of the insulins from the beginning of the glucose clamp to any time point is expressed as a proportion of the total insulin exposure during the entire clamp period (i.e., AUC-insulin$_{0-600}$).*

The relative glucose consumption for each of the insulins (expressed as a proportion of total glucodynamic effect during the entire clamp period, i.e., AUC-GIR$_{0-600}$) at different time points can be seen in Fig. 1*B*. Total glucose consumption over the entire clamp period (AUC-GIR$_{0-600}$) after inhalation of INH (3.03 g/kg) was comparable to both ILP (3.16 g/kg) and RHI (3.44 g/kg). The relative bioefficacy of INH in the first hour after administration was 15% compared with RHI and 10% compared with ILP. The relative bioefficacy of INH over the entire clamp period was 10% vs. RHI or 11% vs. ILP.

Pharmacokinetic results

Total insulin exposure was similar for INH and RHI (14,000 vs. 17,700 $\mu U \cdot ml^{-1} \cdot min^{-1}$), which is consistent with the findings on pharmacodynamics (Fig. 2, Table 2). The time to maximal serum insulin concentration (t_{max}) observed with INH (55 min) was more rapid than that of RHI (148 min; $P < 0.001$). Maximal serum insulin levels (C_{max}) achieved after administration of INH and RHI were similar (66.9 vs. 61.0 μU/ml) (Fig. 2*A*). The relative insulin exposure for INH and RHI (expressed as a proportion of total insulin exposure during the entire clamp period, i.e., AUC-insulin$_{0-600}$) at different time points can be seen in Fig. 2*B*. Comparisons with ILP are not reported due to the possibility of <100% cross-reactivity between human insulin and lispro for the antibody used in the insulin assay. The relative bioavailability of INH compared with RHI in the first 60 min after inhalation was 18%, compared with the total bioavailability over the entire clamp period (600 min) of 9%, reflecting a rapid increase in circulating insulin during this period.

Tolerability

INH was well tolerated by all subjects. No clinically relevant changes in laboratory safety parameters, lung function tests, or other drug-related effects were observed.

CONCLUSIONS — This study demonstrates, through a comparison of the time-action profiles of INH and two insulins administered by subcutaneous injection (ILP and RHI), that the onset of action of INH is at least as fast as ILP (a rapid-acting insulin analog) and considerably faster than RHI. The time-action profile of INH is consistent with previously published studies with inhaled pure (i.e., no absorption enhancers) insulin formulations (1–4). It was also found that the early metabolic response to INH is similar to that of ILP. The insulin doses for comparison in this study were chosen to be equivalent based on an assumed relative efficacy of ~10% (i.e., 1 mg INH ≡ 3 IU subcutaneous insulin). The measured GIR-AUC$_{0-600}$ (showing equivalence for the three insulins at these doses) and the calculated values for total relative bioefficacy (10–11%) demonstrate that this was a valid assumption.

The metabolic activity of INH declined somewhat more slowly than that of ILP but was nominally faster than RHI, which is also consistent with previous studies, irrespective of the presence or absence of absorption enhancers (1–5). The reason for the prolonged metabolic action

Table 2 —*Mean pharmacokinetic summary measures after inhalation of 6 mg INH or subcutaneous injection of 18 U RHI on two different study days in 17 healthy volunteers (baseline values subtracted)*

Serum insulin measures	INH	RHI	Ratio/difference*	90% CI*	*P* values†
Maximal serum insulin concentration (C_{max}) (μU/ml)‡	66.9	61.0	110% (INH/RHI)	86–139	NS
Time to maximal concentration (t_{max}) (min)*	55	148	−93 (INH−RHI)	−132 to −54	<0.001
AUC-Insulin$_{0-60}$ (μU · ml^{-1} · min^{-1})‡	2,740	1,650	166% (INH/RHI)	120–229	<0.05
AUC-Insulin$_{0-180}$ (μU · ml^{-1} · min^{-1})‡	8,390	7,560	111% (INH/RHI)	90–137	NS
AUC-Insulin$_{0-600}$ (μU · ml^{-1} · min^{-1})‡	14,000	17,700	79% (INH/RHI)	67–92	<0.05

*Arithmetic mean; †one-sided for t_{max} and AUC-Insulin$_{0-60}$, two-sided for all other measures; ‡geometric mean.

of inhaled insulin, which is distinctly different from the profile of subcutaneously injected rapid-acting insulin analogs, is not clearly understood. A possible explanation is that the pulmonary absorption of insulin is dependent on the size and, hence, the dissociation rate of the particles and their aggregates (9,10).

The pharmacodynamic findings of this study suggest that INH, with its initial rapid rise in circulating insulin levels, provides an insulin profile closer to the physiologic response to a meal than that which can be achieved after subcutaneous injection of RHI. INH therefore appears to be well suited to cover meal-related insulin requirements.

Several studies involving rapid-acting insulin analogs such as insulin aspart and insulin lispro have consistently demonstrated that a rapid onset of action leads to improvements in postprandial blood glucose control (6,11,12). However, clinical studies have shown that the duration of action of rapid-acting insulin analogs may be too short to provide adequate postprandial control, as indicated by rising glucose levels in the postabsorptive state (13,14). In fact, it has been shown that improved glycemic control could only be achieved with an insulin analog by improving daytime basal insulin therapy (13,14). As INH has a longer duration of action than subcutaneous ILP, it may provide better postprandial glucose control. However, this hypothesis needs to be confirmed.

The observed relative efficacy for INH of 10–11% is comparable to or even greater than previously published results for pure insulin preparations for inhalation (1–4). Until recently, such insulin absorption rates and metabolic effect could only be achieved by means of absorption-facilitating substances (15). It should be emphasized that in terms of the use of INH preparations for meal-related insulin needs, the efficacy of INH is more pronounced than the calculated rate of 10–11%. In the first hour after insulin administration—the pivotal time for prandial blood glucose control—a relatively high metabolic effect is required. The relative bioefficacy of INH during this period was 15% compared with RHI. Nevertheless, improvements in bioefficacy (e.g., through further advances in inhalation device technology) remain a challenge for the future.

The maximal metabolic effect obtained with INH (6 mg) was lower than that of ILP (18 units), although this does not take into account the dose dependence of the metabolic activity. Because an increase in dose of INH may result in a more prolonged duration of action, as has been demonstrated for RHI and ILP (16,17), this needs to be investigated further.

The serum insulin time-concentration (pharmacokinetic) profiles observed after INH or RHI insulin administration reflected the corresponding pharmacodynamic time-action profiles. Although the radioimmunoassay used in the present study was validated at the testing laboratory, the possibility of a mismatch in antibody cross-reactivity for human insulin (inhaled or injected) and insulin lispro remained, because the relative ILP concentrations were consistently greater than those reported in other trials (11,18).

The efficacy and suitability of inhaled insulin has been evaluated in other clinical studies that showed improved glycemic control with inhaled insulin over a period of 3–6 months in patients with type 1 or type 2 diabetes (8,19–21). Moreover, participants in these studies showed a high level of satisfaction with the new route of insulin delivery and the treatment was well tolerated (22,23). The results of long-term clinical studies involving inhaled insulin show satisfactory metabolic control was maintained for up to 4 years by use of preprandial inhaled insulin and no safety issues were reported (24).

In conclusion, inhaled insulin offers the benefits of noninvasive administration and a time-action profile that combines the advantages of both rapid-acting insulin analogs and regular human insulin, making it well suited for prandial insulin substitution.

Acknowledgments— This study was supported by Pfizer (New York, NY) and Aventis Pharmaceuticals (Bridgewater, NJ), who are developing Exubera in conjunction with Nektar Therapeutics (San Carlos, CA).

A preliminary report of this study was presented at the 60th Scientific Sessions of the American Diabetes Association, San Antonio, Texas, 9–13 June 2000, and at the 36th Annual Meeting of the European Association for the Study of Diabetes, Jerusalem, Israel, 17–21 September 2000.

References

1. Heinemann L, Traut T, Heise T: Time–action profile of inhaled insulin. *Diabet Med* 14:63–72, 1997
2. Brunner GA, Balent B, Ellmerer M, Schaupp L, Siebenhofer A, Jendle JH, Okikawa J, Pieber TR: Dose–response relation of liquid aerosol inhaled insulin in type I diabetic patients. *Diabetologia* 44: 305–308, 2001
3. Perera AD, Kapitza C, Nosek L, Fishman RS, Shapiro DA, Heise T, Heinemann L: Absorption and metabolic effect of inhaled insulin: intrapatient variability after inhalation via the Aerodose insulin inhaler in patients with type 2 diabetes. *Diabetes Care* 25:2276–2281, 2002
4. Patton JS, Bukar JG, Eldon MA: Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. *Clin Pharmacokinet*

43:781–801, 2004
5. Steiner S, Pfützner A, Wilson BR, Harzer O, Heinemann L, Rave K: Technosphere/insulin—proof of concept study with a new insulin formulation for pulmonary delivery. *Exp Clin Endocrinol Diabetes* 110:17–21, 2002
6. Heinemann L, Heise T, Wahl LC, Trautmann ME, Ampudia J, Starke AA, Berger M: Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro(B29)] human insulin. *Diabet Med* 13:625–629, 1996
7. Zambanini A, Newson RB, Maisey M, Feher MD: Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract* 46:239–246, 1999
8. Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA: Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Intern Med* 134:203–207, 2001
9. Jendle JH, Karlberg BE: Intrapulmonary administration of insulin to healthy volunteers. *J Intern Med* 240:93–98, 1996
10. Jendle JH, Karlberg BE: Effects of intrapulmonary insulin in patients with non-insulin-dependent diabetes. *Scand J Clin Lab Invest* 56:555–561, 1996
11. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR: [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. *Diabetes* 43:396–402, 1994
12. Heinemann L, Weyer C, Rauhaus M, Heinrichs S, Heise T: Variability of the metabolic effect of soluble insulin and the rapid-acting insulin analog insulin aspart. *Diabetes Care* 21:1910–1914, 1998
13. Del Sindaco P, Ciofetta M, Lalli C, Perriello G, Pampanelli S, Torlone E, Brunetti P, Bolli GB: Use of the short-acting insulin analogue lispro in intensive treatment of type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal. *Diabet Med* 15:592–600, 1998
14. Ciofetta M, Lalli C, Del Sindaco P, Torlone E, Pampanelli S, Mauro L, Chiara DL, Brunetti P, Bolli GB: Contribution of postprandial versus interprandial blood glucose to HbA_{1c} in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care* 22:795–800, 1999
15. Heinemann L, Klappoth W, Rave K, Hompesch B, Linkeschowa R, Heise T: Intra-individual variability of the metabolic effect of inhaled insulin together with an absorption enhancer. *Diabetes Care* 23:1343–1347, 2000
16. Galloway JA, Root MA, Rathmacher RP, Carmichael RH: A comparison of acid regular and neutral regular insulin: responses of normal fasted subjects to varying doses of regular insulin. *Diabetes* 22:471–479, 1973
17. Heinemann L, Woodworth JR: Pharmacokinetics and metabolism of insulin lispro. *Drugs Today* 34 (Suppl. C):23–36, 1998
18. Sapin R: Insulin assays: previously known and new analytical features. *Clin Lab* 49:113–121, 2003
19. Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng SL, Gelfand RA: Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet* 357:331–335, 2001
20. Quattrin T, Bélanger A, Bohannon NJV, Schwartz SL: Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 27:2622–2627, 2004
21. Hollander PA, Blonde L, Rowe R, Mehta AE, Milburn JL, Hershon KS, Chiasson J-L, Levin SR: Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes mellitus: results of a 6-month, randomized, comparative trial. *Diabetes Care* 27:2356–2362, 2004
22. Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA: Treatment satisfaction with inhaled insulin in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Care* 24:1556–1559, 2001
23. Cappelleri JC, Cefalu WT, Rosenstock J, Kourides A, Gerber RA: Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin regimen and a subcutaneous insulin regimen. *Clin Ther* 24:552–564, 2002
24. Skyler J: Sustained long-term efficacy and safety of inhaled insulin (Exubera) during 4 years of continuous therapy (Abstract). *Diabetes* 53 (Suppl. 2):A115, 2004