AIR Inhaled Insulin Versus Subcutaneous Insulin

Pharmacokinetics, glucodynamics, and pulmonary function in asthma

MICHAEL WOLZT, MD[1]
AMPARO DE LA PEÑA, PHD[2]
PIERRE-YVES BERCLAZ, MD[2]
FABIÁN S. TIBALDI, PHD[2]
JEFFREY R. GATES DHSC[2]
DOUGLAS B. MUCHMORE, MD[2]

OBJECTIVE — This study evaluated pharmacokinetic and glucodynamic responses to AIR inhaled insulin relative to subcutaneous insulin lispro, safety, pulmonary function, and effects of salbutamol coadministration.

RESEARCH DESIGN AND METHODS — Healthy, mildly asthmatic, and moderately asthmatic subjects (n = 13/group, aged 19–58 years, nonsmoking, and nondiabetic) completed this phase I, open-label, randomized, crossover euglycemic clamp study. Subjects received 12 units equivalent AIR insulin or 12 units subcutaneous insulin lispro or salbutamol plus AIR insulin (moderate asthma group only) before the clamp.

RESULTS — AIR insulin exposure was reduced 34 and 41% (both $P < 0.01$) in asthmatic subjects (area under the curve$_{0\text{-}t}$, 24.0 and 21.1 nmol · min · l^{-1} in mild and moderate asthma subjects, respectively) compared with healthy subjects (35.2 nmol · min · l^{-1}), respectively. Glucodynamic (G) effects were similar in healthy and mildly asthmatic subjects (G_{tot} = 38.7 and 23.4 g, respectively; P = 0.16) and were reduced in moderately asthmatic subjects (G_{tot} = 10.7 g). Salbutamol pretreatment (moderately asthmatic subjects) improved bioavailability. AIR insulin had no discernable effect on pulmonary function. AIR insulin adverse events (cough, headache, and dizziness) were mild to moderate in intensity and have been previously reported or are typical of studies involving glucose clamp procedures.

CONCLUSIONS — This study suggests that pulmonary disease severity and asthma treatment status influence the metabolic effect of AIR insulin in individuals with asthma but do not affect AIR insulin pulmonary safety or tolerability. In view of the potential interactions between diabetes treatment and pulmonary status, it is prudent to await the results of ongoing clinical trials in diabetic patients with comorbid lung disease before considering the use of inhaled insulin in such patients.

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For >80 years the therapeutic administration of insulin has been primarily limited to the injection route (1). However, in an important treatment landmark, regulatory agencies in the U.S. and Europe recently approved an inhaled insulin delivery system for use in the management of type 1 and type 2 diabetes (2). With the emergence of innovative inhaled insulin systems over the next several years (3), this novel alternative to subcutaneous insulin administration is anticipated to be a durable strategy to improve the quality of life for many patients and potentially eliminate a frequent barrier to effective therapy (4).

The AIR Insulin System (Alkermes, Cambridge, MA) is based on the deep lung delivery of dry-powder aerosols composed of large low-density particles (5). Each individual particle is highly dispersible, of low mass density and high geometric/aerodynamic diameters, and contains the drug and excipient within its matrix, so that no carrier particles are required. AIR insulin has low cohesive forces and can be aerosolized using a simple, breath-actuated inhaler device that requires no additional power.

To date, clinical studies (3,6,7) of inhaled insulin in diabetic patients have demonstrated a consistent pattern of safety and efficacy. However, for patients presenting with comorbidities related to compromised lung function, inhaled insulin safety information is limited, and the influence of lung disease itself on pharmacokinetic and glucodynamic response is not fully understood. In patients with asthma, researchers have postulated that factors such as turbulence, airway obstruction, and altered permeability of the alveolar epithelium might influence the site of deposition and/or absorption of the aerosolized insulin, reducing inhaled insulin bioavailability and biopotency (8–10). The current study was designed to investigate the effect of differing levels of asthma severity (relative to healthy subjects) on the pharmacokinetic and glucodynamic responses to treatment with AIR insulin, compared with treatment with injectable insulin lispro, in nonsmoking nondiabetic subjects. Secondary objectives included safety, tolerability, pharmacokinetic and glucodynamic intrasubject variability of AIR insulin administration, evaluation of pulmonary function relative to insulin dosing, and characterization of the potential effects of salbutamol coadministration (as a pretreatment to AIR insulin therapy) on pharmacokinetic/glucodynamic and pulmonary function.

RESEARCH DESIGN AND METHODS

— Nonsmoking, nondiabetic subjects with or without asthma (between age 19 and 58 years, with a BMI ≤30 kg/m^2, a fasting blood glucose ≤100 mg/dl, and without active pulmonary dis-

From the [1]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; and [2]Eli Lilly and Company, Indianapolis, Indiana.

Address correspondence and reprint requests to Dr. Michael Wolzt, Clinical Pharmacology, Medical University of Vienna, Währinger Gürtel 18-20, Vienna, Austria A-1090. E-mail: michael.wolzt@meduniwien.ac.at.

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Abbreviations: AUC, area under the curve; FEV, forced expiratory volume; FVC, forced vital capacity; GIR, glucose infusion rate; IRI, immunoreactive insulin; PFT, pulmonary function test.

ease) were included in the study. Subjects with asthma were required to fulfill recognized diagnostic classification (11) for either mild persistent asthma or moderate persistent asthma. Subjects with occasional asthma symptoms and forced expiratory volume at 1 s (FEV_1) values ≥80% were classified as having mild persistent asthma. Moderate persistent asthma was characterized by daily asthma symptoms, daily use of short-acting β2-agonists or exacerbations affecting daily activities, and FEV_1 values of >60 to ≤80% or a ≥12% increase in FEV_1 after bronchodilator treatment.

Asthmatic subjects requiring a long-acting β2-agonist or a short-acting β2-agonist other than salbutamol were asked to switch to salbutamol for at least 7 days before the study period to determine whether they were able to sustain such a therapeutic regimen without an exacerbation of asthma symptoms. Subjects were excluded from the study if they had either an upper-respiratory infection or a significant exacerbation of asthma symptoms within the 4-week period preceding the study, used oral corticosteroid during the preceding 3 months, had a history of >20 pack-years of cigarette smoking, or had a serum cotinine level ≥20 ng/ml at the screening visit. A local ethics committee approved the study protocol, and all subjects provided written informed consent before participating in the study.

This phase I, open-label, randomized, cross-over euglycemic glucose clamp study was conducted over a period of ~18 weeks at a single investigative site (Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria). Screening was conducted on two separate occasions to establish pulmonary function stability, to determine a baseline for posttreatment efficacy and safety comparisons, and to evaluate prospective subjects for their capacity to inhale at 30 l/min for 3–5 s with an AIR insulin inhaler device. Following screening, qualified healthy and mildly asthmatic subjects were randomized to one of three treatment sequences and three glucose clamp procedures. Subjects with moderate asthma were randomized to one of four treatment sequences and four glucose clamp procedures. At each visit in which a glucose clamp procedure was performed, a series of bedside spirometry tests were performed, insulin was administered via the inhalation or subcutaneous injection route, and serial blood samples were taken. Treatments included 12 unit equivalents of AIR insulin, supplied as two 6-unit equivalent capsules (2.6 mg insulin/capsule) packaged in foil blister cards and delivered to the deep lung as an aerosol via a hand-held, breath-actuated, inhaler device; or 12 units of subcutaneous insulin lispro (Humalog; Eli Lilly and Company, Indianapolis, IN), supplied in 10-ml vials (100 units/ml). For subjects with moderate asthma, an additional treatment comprised the administration of two inhalations of salbutamol (0.1 mg/inhalation sultanol; GlaxoSmithKline, Vienna, Austria) 1 h before AIR insulin administration.

This study was designed to compare the pharmacokinetic and glucodynamic response to a single fixed dose of AIR insulin in a nondiabetic population with mild persistent or moderate asthma (with and without pretreatment inhaled salbutamol) relative to healthy subjects and to subcutaneous insulin lispro and to explore the within-subject glucodynamic and pharmacokinetic variability of AIR insulin administered using the commercial delivery system. The relative glucodynamic effect of each insulin treatment was assessed using the euglycemic glucose clamp procedure (12). Blood samples for determination of serum immunoreactive insulin (IRI) concentrations for the pharmacokinetic assessment were collected at multiple time points, from predose up to 10 h after dose administration. Treatment safety was determined by means of complete pulmonary function tests (PFTs), which included FEV_1, forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DL_{co}), and total lung capacity. PFTs were performed on subjects (within 24 h) before and after each clamp procedure. Bedside spirometry (FEV_1 and FVC) was performed with the subject in a semirecumbent position at the time of the clamp procedure (at predose, ~30 min postdose, halfway through the clamp, and immediately at the end). Observational data regarding adverse reactions were collected throughout the study.

Glucodynamic, pharmacokinetic, and pulmonary function analyses

Glucodynamic parameters were derived individually for each subject and treatment from raw glucose infusion rate (GIR) data using Microsoft Excel 2003. A locally weighted linear regression model using S-PLUS version 6.2 (Insightful, Seattle, WA) was applied to the pooled raw GIR data to generate plots of smoothed GIR versus time by subject group and treatment. The primary glucodynamic parameters included the total glucose infused (G_{tot}) for the duration of the clamp after drug administration, the maximum GIR (R_{max}), and the time to the maximum GIR (t_{Rmax}).

Serum concentrations of insulin were measured by a radioimmunoassay method validated in the 20–2,500 pmol/l range for the quantitative determination of free serum IRI (MDS Pharma Services, St. Laurent, Quebec City, Canada). Insulin concentration data were analyzed with WinNonlin (professional edition 4.1; Mountain View, CA) using noncompartmental pharmacokinetic analysis. Parameters included the area under the IRI concentration versus time curve from time zero until the IRI concentrations returned to the predose baseline value ($AUC_{0\text{-}t'}$), the maximum IRI concentration (C_{max}), and the time of maximum IRI concentration (t_{max}).

Pulmonary function was analyzed with the Sensor Medics Vmax PFT System (Yorba Linda, CA). Each before/after clamp observation was analyzed separately, with the before clamp observation used as the baseline. Bedside spirometry (Jaeger MasterScope CT; Hoechberg, Germany) data were analyzed separately and summarized descriptively.

Statistical analysis

All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC). The primary pharmacokinetic parameters ($AUC_{0\text{-}t'}$ and C_{max}) were log transformed before analyses. To compare the pharmacokinetic parameters of AIR insulin with subcutaneous insulin lispro a linear mixed-effects model was fitted, with group, treatment, treatment by group, visit, and sequence as fixed effects and subject within group and sequence as a random effects. The log-transformed results were transformed to the original scale by exponentiation to obtain geometric least-squares means, treatment ratios, and 90% CIs for the ratios. For the AIR insulin versus AIR insulin plus salbutamol comparison, another linear mixed-effects model was applied with treatment, visit, and sequence as fixed effects and subject within sequence as a random effect. Glucodynamic parameters were analyzed similarly. Both pharmacokinetic and glucodynamic parameters were summarized using descriptive statistics. To analyze the pharmacokinetic variability of the AIR insulin, a linear mixed-effect

Table 1—*Baseline subject characteristics*

Characteristic	Group		
	Healthy	Mild asthma	Moderate asthma
n	13	13	13
Age (years)	28 ± 7	28 ± 10	34 ± 12
Female/male (%)	46/54	54/46	31/69
Height (cm)	174 ± 8	171 ± 9	175 ± 8
Weight (kg)	68 ± 13	68 ± 11	79 ± 12
BMI (kg/m^2)	23 ± 3	23 ± 3	26 ± 3
FEV_1 (l/s)*	4.0 ± 0.7	3.4 ± 0.7	2.9 ± 0.6
FVC*	4.7 ± 1.0	4.4 ± 1.0	4.5 ± 1.0
FEV_1/FVC*	0.9 ± 0.1	0.8 ± 0.1	0.7 ± 0.1

Data are means ± SD, unless otherwise indicated. *n = 11.

model was applied with group and visits as fixed effects and subject (group sequence) as a random effect.

The effect of PFT parameters on pharmacokinetic and glucodynamic parameters was explored using a linear mixed-regression model, fitted on the logarithm of pharmacokinetic or pharmacodynamic parameters with PFTs as covariates. The model included treatment, group, and the corresponding interaction terms; the subject was included as a random effect.

RESULTS — Of 39 subjects who entered the trial and received at least one dose of the study drugs, 36 subjects completed the study. One subject (healthy group) was unable to perform bedside spirometry during clamp procedure and was therefore discontinued. Another subject (mild asthma group) was discontinued by the investigator due to the subject's inability to adequately employ the inhalation system, thus disqualifying that subject from fulfilling bedside spirometry protocol requirements. Finally, a subject (moderate asthma group) was discontinued by the investigator due to a worsening of asthma on the day that the clamp procedure was performed. None of these events were qualified as adverse drug reactions. A summary of the baseline demographic and clinical characteristics of the subjects, which includes all subjects exposed to at least one dose of the study drugs, is presented in Table 1.

Pharmacokinetic exposure and glucodynamic effect

AIR insulin was rapidly absorbed in all subject groups, as evidenced by median t_{max} values that were comparable across all subject groups, and was similar to subcutaneous insulin lispro (Table 2). Following the administration of 12 units equivalent AIR insulin, subjects with mild and moderate persistent asthma demonstrated mean overall insulin exposure ($AUC_{0\text{-}t'}$) that was ~34 and 41% (both $P \leq 0.01$) lower, respectively, compared with that in healthy subjects (Table 2; Fig. 1). Following the administration of 12 units of subcutaneous insulin lispro, subjects with mild and moderate persistent asthma demonstrated mean overall insulin exposure ($AUC_{0\text{-}t'}$) that was not statistically different from that observed in healthy subjects (P = 0.69 and 0.86, respectively) (Table 2; Fig. 1). Pharmacokinetic ($AUC_{0-t'}$) intrasubject variability (CV%) for AIR insulin was observed in the subject groups as follows: healthy, 32.1%; mild asthma, 49.1%; and moderate asthma, 68.4%. Post hoc analysis indicated that pharmacokinetic ($AUC_{0\text{-}t'}$) intrasubject variability was not statistically different between mild asthma and healthy subjects (P = 0.092), but moderate asthma subjects did demonstrate more variability as compared with healthy subjects (P = 0.014). Pharmacodynamic (G_{tot}) intrasubject variability (CV%) for AIR insulin for the same respective groups was healthy, 33.8%; mild asthma, 73.7%; and moderate asthma, 77.1%. Post hoc analyses of intrasubject variability indicated that both asthma types showed greater pharmacodynamic (G_{tot}) variability compared with healthy subjects (P = 0.01).

In mild asthmatic subjects, the glucodynamic response (G_{tot}) to AIR insulin was not significantly different from that seen in healthy subjects (P = 0.16). In moderate asthmatic subjects, AIR insulin

Table 2—*Summary of pharmacokinetic and glucodynamic results by subject group and treatment*

	Healthy		Mild asthma		Moderate asthma		
	AIR	Subcutaneous lispro	AIR	Subcutaneous lispro	AIR	Subcutaneous lispro	AIR + salbutamol
Pharmacokinetic							
N_{PK}*	25	13	26	11	22	12	11
$AUC_{0\text{-}t'}$ (nmol · min/l)	35.2 (46.1)	61.1 (25.4)	24.0 (59.5)	65.2 (26.6)	21.1 (74.8)	59.5 (17.1)	31.3 (36.8)
C_{max} (pmol/l)	248 (46.0)	421 (38.7)	185 (41.3)	432 (36.8)	183 (29.0)	374 (35.8)	221 (27.0)
t_{max} (min)	50 (11–131)	48 (34–64)	51 (12–124)	62 (32–125)	48 (12–124)	62 (32–191)	60 (22–121)
Glucodynamic							
N_{GD}*	25	12	25	10	18	11	10
G_{tot} (g)	38.7 (108.0)	59.7 (43.6)	23.4 (156.0)	73.5 (33.2)	10.7 (159.0)	47.8 (88.5)	15.5 (180.0)
R_{max} (mg/min)	355 (59.5)	471 (30.8)	290 (70.1)	526 (41.8)	183 (68.3)	401 (56.1)	261 (69.5)
t_{Rmax} (min)	47 (33–174)	79 (44–130)	47 (26–104)	67 (25–153)	52 (3–132)	81 (46–184)	62 (34–110)

Data are geometric means (coefficients of variation) (%); median (range) are shown for t_{max} and t_{Rmax}. C_{max}, maximum serum insulin concentration; GD, glucodynamics; G_{tot}, total amount of glucose infused throughout the clamp; N_{GD}, number of GD observations; N_{PK}, number of PK observations; PK, pharmacokinetics; R_{max}, maximum glucose infusion rate; t_{max}, time to maximum insulin concentration; t_{Rmax}, time to maximum glucose infusion rate. *Differences in number of observations between N_{PK} and N_{GD} by group for a given parameter are due to incomplete (due to either discontinuations or noncomputable data) or outlying data.

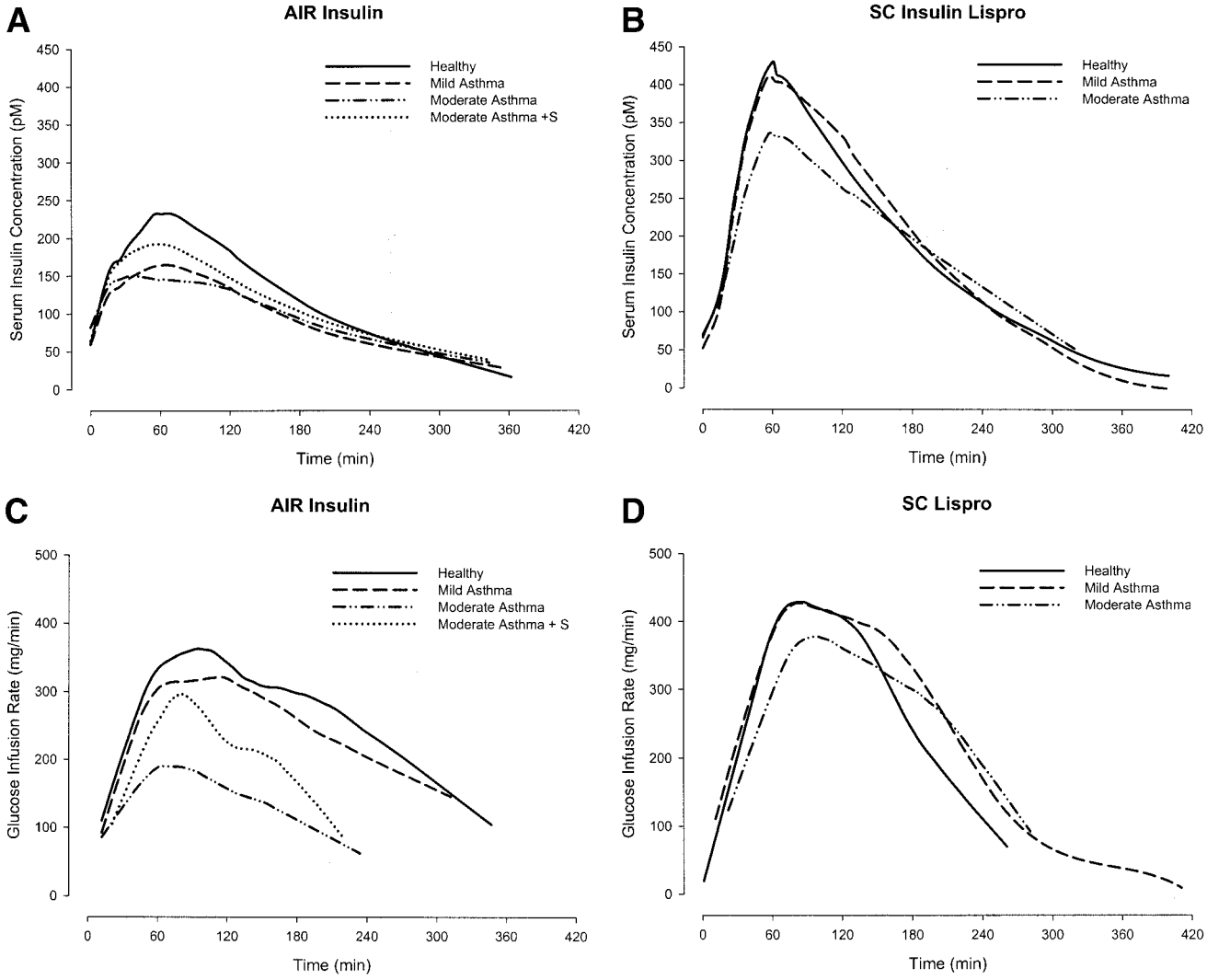

Figure 1—*Serum insulin concentration* (A *and* B) *and glucose infusion rates* (C *and* D) *versus time, by treatment across subject groups after administration of 12 units equivalent AIR insulin or 12 untis insulin lispro.*

therapy was associated with reduced overall effect (72% lower relative to healthy subjects, $P < 0.01$). Subcutaneous insulin lispro administration resulted in glucodynamic responses in mild and moderate asthmatic subjects who were not significantly different from healthy subjects ($P = 0.55$ and 0.14, respectively). Subjects with moderate asthma pretreated with salbutamol experienced an approximate 50% increase in both overall inhaled insulin exposure and metabolic response (both $P < 0.05$) compared with AIR insulin treatment alone.

There was no statistical evidence of an association between any of the PFTs and AUCs ($P = 0.53$ for FEV_1 and FVC and $P = 0.14$ for DL_{co}) or C_{max} ($P = 0.65$ for FEV_1, $P = 0.22$ for FVC, and $P = 0.27$ for DL_{co}). However, there was a relationship between PFTs (FEV_1 and FVC) and G_{tot}, as well as R_{max} ($P < 0.01$ for all). Finally, a statistically significant association was noted between DL_{co} and R_{max} ($P < 0.05$) but not for G_{tot} ($P = 0.177$).

Safety

AIR insulin was well tolerated by both healthy subjects and subjects with mild persistent or moderate asthma. No significant treatment group differences were noted for either bedside spirometry during the clamp procedure (FEV_1 and FVC) or PFTs performed a day before/after clamps. Treatment-emergent adverse events, possibly related to AIR insulin, were noted by the investigator in 25% (9 of 36) of the study population (commonly cough, headache, and dizziness). These events were mild to moderate in intensity and have been reported in previous studies (13–15) or are typical of insulin studies involving glucose clamp procedures. No treatment-emergent adverse events were reported for subcutaneous insulin lispro. No deaths or other serious adverse events occurred during this study, and no clinically significant changes were noted in safety laboratory parameters, vital signs, or electrocardiograms.

CONCLUSIONS — Results from this trial demonstrated the tolerability and rapid absorption of AIR insulin in healthy subjects and in subjects with mild and moderate asthma. In subjects with mild and moderate persistent asthma, overall insulin exposure was significantly reduced with AIR inhaled insulin treatment. In contrast, subjects treated with subcutaneous insulin lispro demonstrated comparable exposure across the three different treatment groups. A differ-

ential effect of asthma severity on the glucodynamic response to the two treatments was also observed in this study. In mildly asthmatic subjects, the glucodynamic response to AIR insulin treatment was comparable with that seen in healthy subjects, whereas the glucodynamic response was significantly reduced in subjects with moderate asthma in the absence of salbutamol pretreatment. In contrast, the glucodynamic response to insulin lispro treatment was not statistically significantly different across all subject groups. Upon review of the overall pharmacokinetic and glucodynamic results, one may speculate that compared with healthy subjects, patients with moderate asthma have some degree of systemic insulin resistance (potentially based on body weight differences, nonspecific stress factors, prior use of corticosteroids, etc.), but this study was not powered to definitively demonstrate such a conclusion. This study also demonstrated that salbutamol pretreatment significantly increased AIR insulin exposure and action toward that seen in healthy subjects. Intrasubject variability was generally higher in asthmatic subjects compared with healthy subjects.

Comparison of intrasubject variability of AIR insulin to injected insulin lispro pharmacokinetic and pharmacodynamic responses were not tested in this study but have been shown to be comparable in a previous study of healthy volunteers (7). The study by Rave et al. (2005) provided the basis for the labeling of the 2.6-mg AIR insulin capsule as being 6 units equivalent. The relative bioavailability and biopotency estimate obtained in that study were intrinsically imprecise (coefficient of variation values for pharmacokinetic parameters were in the range of 62–72%). In the current study, the pharmacokinetic and glucodynamic responses in healthy volunteers to 12 units equivalent of AIR insulin were lower than those seen in response to 12 units of injected insulin lispro (Table 2). It remains uncertain whether this difference between studies in healthy volunteers represents random or systematic variation. Limited information has been published regarding the impact of asthma on inhaled insulin pharmacokinetic and/or glucodynamic parameters. Henry et al. (16), using an aerosol of aqueous insulin, reported significantly reduced insulin exposure and reduced glucose effects in mild-to-moderate asthmatic subjects compared with a healthy group. In our study, mild and moderate asthma groups had similar reductions in inhaled insulin exposure, though differing glucose effects, relative to healthy subjects. Such a response would suggest that there is a relative insulin resistance in moderate asthmatic subjects.

Teeter et al. (17) reported reduced pulmonary absorption of dry-powder inhaled insulin in mild-to-moderate asthmatic subjects; however, treatment with albuterol (the U.S. generic terminology for salbutamol) improved inhaled insulin mean maximum insulin concentration and AUC (~25–35% in mild asthma; ~45–50% in moderate asthma) to levels comparable with healthy nonasthmatic subjects. Our results with salbutamol pretreatment (about 50% improvement in insulin exposure in moderate asthma) are remarkably similar.

In this study it was observed that the overall and peak pharmacokinetic exposures were significantly decreased in the asthma groups. While this might suggest that there may be a correlation between the presence of lung disease and pharmacokinetics, formal analysis has failed to show a relationship between pharmacokinetics and PFTs. The significant relationship between PFTs and glucodynamic, but not pharmacokinetic parameters, may suggest that there is a relationship between the lung disease process and insulin sensitivity. However, PFTs are not a validated predictor of absorption in subjects with asthma.

In conclusion, our findings may have important clinical implications for inhaled insulin usage in diabetic patients with coexisting asthma. This study has demonstrated that severity of asthma in nondiabetic individuals impacts the exposure and action of inhaled insulin, and short-acting bronchodilator pretreatment can acutely modulate these effects. We excluded long-acting β agonist treatments from this trial, and thus cannot comment on their potential to alter inhaled insulin exposure and action. Results from this study have demonstrated the safety and tolerability of AIR insulin in both healthy and asthmatic subjects and support further evaluation of its use in asthma patients with diabetes; however, in view of the potential interactions between pulmonary status and diabetes treatment, it remains prudent to await results of ongoing inhaled insulin clinical trials in diabetic patients with comorbid lung disease before considering use of inhaled insulin treatment in this population.

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