AIR® Inhaled Insulin versus Subcutaneous Insulin: Pharmacokinetics, Glucodynamics, and Pulmonary Function in Asthma

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**Running Title:** AIR® Insulin pharmacokinetics

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ABSTRACT

Objective: This study evaluated pharmacokinetic and glucodynamic responses to AIR® inhaled insulin relative to subcutaneous insulin lispro, safety, pulmonary function, and effects of salbutamol co-administration.

Research Design And Methods: Healthy, mild asthmatic, and moderate asthmatic subjects (n=13/group; age 19–58 years; nonsmoking; nondiabetic) completed this phase I, open-label, randomized, crossover euglycemic clamp study. Subjects received 12U-equivalent AIR Insulin, or 12U subcutaneous insulin lispro, or salbutamol+AIR Insulin (moderate asthma group only) prior to clamp.

Results: AIR Insulin exposure was reduced 34% and 41% (both P<0.01) in asthmatic subjects (AUC_{0-t}, 24.0 and 21.1 nmol·min/L in mild and moderate subjects, respectively), relative to healthy subjects (35.2 nmol·min/L). Glucodynamic effects were similar in healthy and mild asthmatic subjects (G_{tot} 38.7 and 23.4 g respectively, P=0.16), and reduced in moderate asthmatic subjects (G_{tot} 10.7 g). Salbutamol pretreatment (moderate 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.
For over 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 several 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 (AIR® is a registered trademark of Alkermes Inc., Cambridge, MA) is based upon 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 of inhaled insulin in diabetic patients have demonstrated a consistent pattern of safety and efficacy (3,6,7). 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 (PK) and glucodynamic (GD) 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 PK and GD response to treatment with AIR Insulin, compared with treatment with injectable insulin lispro, in nonsmoking nondiabetic subjects. Secondary objectives included safety, tolerability, PK and GD 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 PK/GD and pulmonary function.

RESEARCH DESIGN AND METHODS

Patient selection. Nonsmoking, nondiabetic subjects with or without asthma, between the ages of 19–58 years, with a body mass index (BMI) ≤ 30 kg/m² and a fasting blood glucose ≤ 100mg/dL, and without active pulmonary disease 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 FEV1 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 FEV1 values of >60% to ≤ 80% or ≥ 12% increase in FEV1 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 if 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, or had a history of >20 pack-years of cigarette smoking or a serum cotinine level \( \geq 20 \text{ ng/mL} \) at the screening visit. A local ethics committee approved the study protocol, and all subjects provided written informed consent prior to participating in the study.

**Study design.** This phase I, open-label, randomized, crossover euglycemic glucose clamp study was conducted over a period of approximately 18 weeks at a single investigative site (Department of Clinical Pharmacology, Medical University of Vienna, Austria). Screening was conducted on two separate occasions to establish pulmonary function stability, to determine a baseline for post-treatment efficacy and safety comparisons, and to evaluate prospective subjects for their capacity to inhale at 30 L/min for 3–5 seconds 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: 12U-equivalents of AIR Insulin, supplied as two 6U-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 12U of subcutaneous insulin lispro (Humalog, Eli Lilly and Company, Indianapolis, IN), supplied in 10mL vials (100 U/mL). For subjects with moderate asthma, an additional treatment comprised the administration of two inhalations of salbutamol (0.1 mg / inhalation; Sultanol®, GlaxoSmithKline, Austria) 1 hour before AIR Insulin administration.

**Study parameters.** This study was designed to compare the PK and GD response to a single fixed dose of AIR Insulin in a non-diabetic 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 GD and PK variability of AIR Insulin administered using the commercial delivery system. The relative GD 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 PK assessment were collected at multiple time points, from predose up to 10 hours after dose administration. Treatment safety was determined by means of complete pulmonary function tests (PFTs), which included forced expiratory volume at 1 second (FEV\(_1\)), forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DLco), and total lung capacity. PFTs were performed on subjects (within 24 hours) before and after each clamp procedure. Beside spirometry (FEV\(_1\) and FVC) was performed with the subject in a semi-recumbent position at the time of the clamp procedure (at predose, approximately 30 min postdose, half-way 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 LOESS fit using S-PLUS™ Version 6.2 (Insightful, Seattle, Washington, USA) was applied to the pooled raw GIR data to generate plots of smoothed GIR versus time by subject group and treatment. The
primary GD parameters included the total glucose infused (Gtot) for the duration of the clamp after drug administration, the maximum GIR (Rmax), and the time to the maximum GIR (tRmax).

Serum concentrations of insulin were measured by a radioimmunoassay method validated in the 20.0 pmol/L to 2500.0 pmol/L range, for the quantitative determination of free serum IRI (MDS Pharma Services, St. Laurent QC, Canada). Insulin concentration data were analyzed with WinNonlin® (Professional Edition 4.1, Mountain View, CA) using noncompartmental PK 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-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 was analyzed separately and summarized descriptively.

Statistical analysis. All statistical analyses were performed using SAS® Version 8.2 (SAS Institute, Inc., Cary, North Carolina). The primary PK parameters (AUC_{0-t'} and C_{max}) were log-transformed prior to analyses. To compare the PK 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 effect. The log-transformed results were transformed to the original scale by exponentiation to obtain geometric least squares means, treatment ratios, and 90% confidence intervals for the ratios. For the AIR Insulin versus AIR Insulin+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 PK and GD parameters were summarized using descriptive statistics. To analyze the PK variability of the AIR Insulin, a linear mixed effect model was applied with group and visits as fixed effects, and subject (group sequence) as a random effect.

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

RESULTS

Of the 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 12U-equivalent AIR Insulin, subjects with mild and moderate persistent asthma demonstrated mean overall insulin exposure (AUC$_{0-t'}$) that was approximately 34% and 41% (both P < 0.01) lower respectively, compared with that in healthy subjects (Table 2, Fig. 1). Following the administration of 12U of subcutaneous insulin lispro, subjects with mild and moderate persistent asthma demonstrated mean overall insulin exposure (AUC$_{0-t'}$) 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 PK (AUC$_{0-t'}$) 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 to 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, as compared to healthy subjects (P=0.01).

In mild asthmatic subjects, the GD 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 therapy was associated with reduced overall effect (72% lower relative to healthy subjects, P < 0.01). Subcutaneous insulin lispro administration resulted in GD responses in mild and moderate asthmatic subjects that were not significantly different from healthy subjects (P = 0.55 and P = 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 AUC (P = 0.53 for FEV$_1$ and FVC; P = 0.14 for DL$_{co}$) or C$_{max}$ (P = 0.65 for FEV$_1$; P = 0.22 for FVC; 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 (TEAEs), possibly related to AIR Insulin, were noted by the investigator in 25% (9/36) 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 TEAEs 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 ECGs.

**DISCUSSION**

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 differential effect of asthma severity on the GD response to the two treatments was also observed in this study. In mild asthmatic subjects, the GD response to AIR Insulin treatment was comparable to that seen in healthy subjects, whereas the GD response was significantly reduced in subjects with moderate asthma in the absence of salbutamol pretreatment. In contrast, the GD response to insulin lispro treatment was not statistically significantly different across all subject groups. Upon review of the overall PK and GD 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 PK and PD responses were not tested in this study but have been shown to be comparable in a previous study of healthy volunteers (7). This study by Rave et al. (2005) provided the basis for 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 (CV values for PK parameters were in the range of 62-72%). In the current study, the PK and GD responses in healthy volunteers to 12 U-eq of AIR insulin were lower than those seen in response to 12 U 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 PK and/or GD 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 area under the curve (approximately 25–35% in mild asthma; approximately 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 PK 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 PK, formal analysis has failed to show a relationship between PK and PFTs. The significant relationship between PFTs and GD, but not PK 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 that short-acting bronchodilator pretreatment can acutely modulate these effects. We excluded long-acting beta 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.

ACKNOWLEDGMENTS
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REFERENCES

### TABLE 1. Baseline subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy (n=13)</th>
<th>Mild Asthma (n=13)</th>
<th>Moderate Asthma (n=13)</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>28 ± 7</td>
<td>28 ± 10</td>
<td>34 ± 12</td>
</tr>
<tr>
<td>Female / Male (%)</td>
<td>46 / 54</td>
<td>54 / 46</td>
<td>31 / 69</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 8</td>
<td>171 ± 9</td>
<td>175 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 13</td>
<td>68 ± 11</td>
<td>79 ± 12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 3</td>
<td>23 ± 3</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>FEV(_1) (L/sec) (^a)</td>
<td>4.0 ± 0.7</td>
<td>3.4 ± 0.7</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>FVC (^a)</td>
<td>4.7 ± 1.0</td>
<td>4.4 ± 1.0</td>
<td>4.5 ± 1.0</td>
</tr>
<tr>
<td>FEV(_1)/FVC (^a)</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD, except where noted otherwise. Abbreviations: FEV\(_1\)= forced expiratory volume at 1 s; FVC= forced vital capacity; \(^a\) \(n=11\).
TABLE 2. Summary of pharmacokinetic and glucodynamic results by subject group and treatment

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Mild Asthma</th>
<th>Moderate Asthma</th>
<th>AIR® + SC lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIR® SC lispro</td>
<td>AIR® SC lispro</td>
<td>AIR® SC lispro</td>
<td>AIR® SC lispro SC lispro</td>
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<td>Pharmacokinetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N_{PK})</td>
<td>25</td>
<td>13</td>
<td>26</td>
<td>11</td>
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<tr>
<td>(AUC_{0-t'})</td>
<td>35.2</td>
<td>61.1</td>
<td>24.0</td>
<td>65.2</td>
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<tr>
<td></td>
<td>(46.1)</td>
<td>(25.4)</td>
<td>(59.5)</td>
<td>(26.6)</td>
</tr>
<tr>
<td>(C_{max})</td>
<td>248</td>
<td>421</td>
<td>185</td>
<td>432</td>
</tr>
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<td></td>
<td>(46.0)</td>
<td>(38.7)</td>
<td>(41.3)</td>
<td>(36.8)</td>
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<tr>
<td>(t_{max})</td>
<td>50</td>
<td>48</td>
<td>51</td>
<td>62</td>
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<tr>
<td>Glucodynamic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(N_{GD})</td>
<td>25</td>
<td>12</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>(G_{tot})</td>
<td>38.7</td>
<td>59.7</td>
<td>23.4</td>
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<td></td>
<td>(108.0)</td>
<td>(43.6)</td>
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<td>(R_{max})</td>
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<td></td>
<td>(59.5)</td>
<td>(30.8)</td>
<td>(70.1)</td>
<td>(41.8)</td>
</tr>
<tr>
<td>(t_{R_{max}})</td>
<td>47</td>
<td>79</td>
<td>47</td>
<td>67</td>
</tr>
</tbody>
</table>

Results are expressed in terms of geometric means (except where indicated), with coefficients of variation (%) enclosed in parentheses below the mean value.

Abbreviations: AIR® = AIR Inhaled Insulin (Alkermes Inc., Cambridge, MA); AUC\(_{0-t'}\) = area under the serum insulin concentration curve from time 0 until time of return to baseline; \(C_{max}\) = 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; $R_{\text{max}}$ = maximum glucose infusion rate; SC = subcutaneous; $t_{\text{max}}$ = time to maximum insulin concentration; $t_{R_{\text{max}}}$ = 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 non-computable data) or outlying data.

† Median (range)
FIGURE LEGEND

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

A. AIR Insulin

B. SC Insulin Lispro

C. AIR Insulin

D. SC Lispro