

Inhaled Insulin Using the AERx Insulin Diabetes Management System in Healthy and Asthmatic Subjects

ROBERT R. HENRY, MD¹
 SUNDER R.D. MUDALIAR, MD¹
 WILLIAM C. HOWLAND III, MD²
 NEELIMA CHU, MD¹

DENNIS KIM, MD¹
 BOB AN, PHD³
 RICKEY R. REINHARDT, MD, PHD³

OBJECTIVE — The AERx insulin Diabetes Management System (AERx iDMS) (Aradigm, Hayward, CA) delivers an aerosol of liquid human insulin to the deep lung for systemic absorption. This study examined the effects on pulmonary function, pharmacokinetics, and pharmacodynamics of inhaled insulin in asthmatic and nonasthmatic subjects without diabetes.

RESEARCH DESIGN AND METHODS — A total of 28 healthy and 17 asthmatic (forced expiratory volume during the first second [FEV₁] 50–80% of predicted value) subjects were enrolled in a two-part, open-label trial. To assess insulin pharmacokinetics and pharmacodynamics, a single inhalation dose of 1.57 mg (45 IU) was given on each of the 2 dosing days in part 1. A dose of 4.7 mg (135 IU) of insulin was inhaled in part 2 to assess effects on pulmonary function.

RESULTS — Inhaled insulin showed area under the curve (AUC)_(0–360 min) values that were significantly greater for healthy subjects than for asthmatic subjects ($P = 0.013$), whereas no difference was observed for maximum concentration (C_{max}) in the two groups. A greater reduction of serum glucose as indicated by area over the curve (AOC)_(0–360 min) was observed in healthy subjects ($P = 0.007$). Asthmatic subjects had greater intrasubject variations in insulin AUC_(0–360 min) and C_{max} values than healthy subjects, but similar variations in glucose AOC_(0–360 min). No significant changes in FEV₁, forced vital capacity (FVC), and FEV₁/FVC were observed from pre- to postdose times, and there were no observed safety issues.

CONCLUSIONS — After inhaling insulin using the AERx iDMS, asthmatic subjects absorbed less insulin than healthy subjects, resulting in less reduction of serum glucose. No effects on airway reactivity were observed. Diabetic patients with asthma may need to inhale more insulin than patients with normal respiratory function in order to achieve similar glycemic control.

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Intensive insulin therapy has been demonstrated to reduce long-term complications in patients with type 1 and type 2 diabetes (1,2). When used as a mealtime

insulin in a basal/bolus regimen, short- or rapid-acting insulin significantly improved postprandial glycemic control, with less incidence of hypoglycemia (3–

7). Many patients object to multiple daily injection and therefore often receive a less-than-maximal benefit of insulin therapy.

The AERx insulin Diabetes Management System (AERx iDMS) was developed by Aradigm (Hayward, CA) as a pulmonary drug delivery system for liquid formulations of insulin (8,9). The AERx iDMS produces a fine droplet aerosol (mass median aerodynamic diameter of ~2–3 μm) from disposable insulin strips, by extruding a prepackaged solution through hundreds of laser-drilled holes in a single-use nozzle (10). The rapid onset of action of inhaled insulin is very similar to rapid-acting insulin analogs (11–13). The availability of a noninvasive delivery system that achieves rapid absorption of insulin into the circulation would be beneficial for administering mealtime insulin. Such a system would allow insulin therapy to more closely mimic the endogenous insulin release of a normal individual and would hopefully improve patient compliance with therapy.

Initial safety, pharmacokinetic (PK), and pharmacodynamic (PD) studies with the AERx iDMS have been conducted in patients with type 1 diabetes. Published results from a clinical trial in 18 type 1 diabetic patients using the AERx iDMS showed that the time at which concentration is maximal (T_{max}) for inhaled insulin (49–65 min) was shorter than that for subcutaneous administration (119 min). The results indicated a clear dose-response relationship between inhaled insulin doses and PK/PD parameters (11). Published studies using other inhalation devices also suggested that pulmonary delivery of insulin improves glycemic control to a similar extent as subcutaneous insulin injection and that inhaled insulin is well tolerated (14,15).

To ensure optimal delivery of insulin into the deep lung, however, the patient's inspiratory profile must be within specified flow/volume parameters before extrusion can occur (9,16,17). Early studies

From the ¹VA San Diego Healthcare System, Section of Diabetes/Endocrinology, San Diego, California; ²HealthQuest Research, Austin, Texas; and ³Novo Nordisk Pharmaceuticals, Princeton, New Jersey.

Address correspondence and reprint requests to Robert R. Henry, Section of Diabetes/Endocrinology, VA San Diego Healthcare System, 3350 La Jolla Village Dr. (111G), San Diego, CA 92161. E-mail: rhenry@vapop.ucsd.edu.

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D.K. is employed by and holds stock in Amylin Pharmaceuticals.

Abbreviations: AERx iDMS, AERx insulin Diabetes Management System; AOC, area over the curve; AUC, area under the curve; C_{max} , maximum concentration; CV, coefficient of variation; ECG, electrocardiogram; FEV₁, forced expiratory volume during the first second; FVC, forced vital capacity; LS, least square; MS, most square; PD, pharmacodynamics; PFT, pulmonary function test; PK, pharmacokinetics; T_{max} , time at which concentration is maximal; URI, upper respiratory tract infection.

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

demonstrated that the PK and PD parameters of inhaled insulin using the AERx iDMS were affected by certain respiratory maneuvers. Significantly less insulin absorption was observed when aerosol delivery occurred during a shallow inspiration (16). Subjects with asthma are a typical population with altered pulmonary function. The distribution and absorption of inhaled insulin could be affected by the degree of airflow obstruction and other pathophysiological changes in patients with asthma. Airway hyper-reactivity of these subjects is another issue of possible concern, since the airways could potentially react to insulin.

The purpose of this study was to examine 1) effects of inhaled insulin on pulmonary function and 2) the PK/PD of inhaled insulin in asthmatic nondiabetic subjects. The results of this study will provide useful information for dosing in asthmatic diabetic patients who may choose to use the AERx iDMS.

RESEARCH DESIGN AND METHODS

This study was an open-label, two-part, parallel-group study in healthy subjects and in subjects with chronic asthma (both groups were nondiabetic). The study was conducted at three centers in the U.S.: VA San Diego Healthcare System, San Diego, California; Phoenix International Life Science, Cincinnati, Ohio; and Health Quest Research, Austin, Texas. The protocols were approved by an appropriately constituted institutional review board at each center before trial initiation. Written informed consent was obtained before trial procedures.

Subjects

The subjects were male and female non-smokers (for at least 12 months, negative urine cotinine at screening) within the ages of 18–45 years who weighed 60–90 kg (men) or 50–90 kg (women). The subjects were divided into two treatment groups: healthy subjects with normal pulmonary function (18,19) (forced vital capacity [FVC], forced expiratory volume during the first second [FEV₁] >85%, and FEV₁/FVC >75% predicted) and subjects with chronic asthma. The subjects with asthma had a clinical history of at least 1 year of intermittent or persistent symptoms, had an FEV₁ ≥50% and ≤80% while withholding β -agonist treatment for 6 h, showed evidence of revers-

ible airway obstruction (an increase in FEV₁ ≥12% between 20 and 30 min after inhaled β -agonist administration), and were presently taking only short-acting inhaled β -adrenergic agonists or an anticholinergic inhalant for treatment of asthma.

Subjects were excluded from the study if they had a pulmonary disorder (including bronchiectasis and chronic bronchitis but not asthma), were treated in an emergency room for asthma within 1 month, were hospitalized for asthma within 3 months before the study, or had unresolved upper respiratory tract infection (URI) within 3 weeks before screening. Subjects were also excluded if they had taken oral, intravenous, intra-articular, or intramuscular corticosteroids (within 12 weeks); inhaled corticosteroids (within 4 weeks); oral, inhaled, or nasal cromolyn or nedocromil; oral or inhaled long-acting β -adrenergic agonists; theophylline therapy; or Montelukast therapy (within 1 week). Female subjects who were pregnant, nursing, or unwilling to use adequate contraceptive measures were excluded.

Trial products

Each insulin strip (Aradigm) contained 45 μ l human insulin inhalation solution, with a regular human insulin concentration of 1,000 IU/ml (45 IU, 1.57 mg) or 1,500 IU/ml (67.5 IU, 2.35 mg). The strips were specifically designed to be used with the AERx iDMS device for insulin inhalation. Due to insulin deposition in the device and the respiratory tract, one insulin strip containing 1.57 mg (45 IU) regular human insulin was anticipated to provide approximately the same glucose lowering effect as 6 IU of subcutaneous regular human insulin. Likewise, each strip containing 2.35 mg (67.5 IU) insulin corresponded to 8.5 IU s.c. insulin.

Treatments and Assessments

The study design consisted of two main parts. In the first part, PK/PD parameters were assessed. In the second part, a larger dose of insulin was inhaled to assess the impact, if any, of inhaled insulin on pulmonary function. PK and PD parameters were not assessed during the second part.

In part 1 of the study, a single inhaled dose of 1.57 mg (45 IU) insulin was administered to fasting healthy and asthmatic subjects on dosing days 1 and 2,

using the AERx iDMS. Asthmatic subjects were not to receive any asthma medication the morning of dosing. Serum insulin, C-peptide, and blood glucose levels were measured at 20 time points from time 0 to 360 min postdose, and the mean values for dosing days 1 and 2 at each time point were used to generate insulin and blood glucose profiles. Pulmonary function tests were performed at 30 min before dosing and 360 min after dosing. In part 2, an inhaled dose of 4.7 mg (135 IU) insulin (two 67.5 IU insulin strips) was administered to healthy and asthmatic subjects in two consecutive inhalations, along with 16 oz (453 g) of Sustacal (Mead Johnson Nutritional, Evansville, IN) to prevent hypoglycemia. Pulmonary function tests were performed at 30 min before dosing and 15, 60, and 360 min after dosing to assess the pulmonary safety of inhaled insulin.

Serum insulin and C-peptide levels were analyzed using an enzyme-linked immunosorbent assay standard commercial kit from DAKO (Carpinteria, CA). Blood glucose was measured with a Yellow Springs blood glucose analyzer (YSI, Yellow Springs, OH). From serum insulin profiles, AUC_(0–360 min), C_{max}, AUC_(0–120 min), AUC_(120–240 min), AUC_(240–360 min), C_{min}, and T_{max} were determined. From blood glucose profiles, AOC_(0–360 min), C_{min}, and T_{min} were determined.

Adverse events, pulmonary function tests, hypoglycemic events, vital signs, physical examinations, clinical laboratory tests, and electrocardiograms (ECGs) were monitored for safety assessments. Pulmonary function tests were performed at screening visits, pre- and postdose on every dosing day, and at follow-up visits to evaluate the effect of inhaled insulin on pulmonary function.

Statistical methods

Because the C-peptide levels and body weight at baseline were different for the healthy and asthmatic groups, the PK parameters were calculated using C-peptide and body weight-adjusted insulin concentrations (20–22). Adjusted insulin concentrations were derived as follows:

Adjusted insulin at time $t = \{ \text{actual insulin at time } t - [(\text{C-peptide at time } t / \text{C-peptide at baseline}) \times \text{actual insulin at baseline}] \} \times \text{body weight}$, where the baseline value was the average of those at predoses and dosing time. The adjusted

insulin value was set to zero if the calculated value was negative.

Natural log-transformed $AUC_{(0-360 \text{ min})}$ and $C_{\max}$ values for PKs and $AOC_{(0-360 \text{ min})}$ values for PDs were analyzed using an ANOVA model with repeated measures over the dosing day. The ANOVA model contained the following effects: group, patient within group, dosing day, and group $\times$ dosing day. The group effect was tested using "patient within group" as an error term. The 90% CIs for geometric mean ratio were calculated using the least square (LS) and most square (MS) (patient within group) means derived from the above-mentioned ANOVA model. Descriptive statistics based on raw data for other PK/PD variables were computed to provide supportive information.

For each study group, intrasubject variability was estimated by the coefficient of variation (CV) (23). All statistical analyses were conducted using SAS (SAS Institute, Cary, NC) version 6.12.

RESULTS

Subject demographics

A total of 45 subjects (28 healthy and 17 asthmatic) were enrolled, and 43 subjects completed both parts of the study. One subject in the healthy group was withdrawn because of folliculitis. Another subject in the asthma group was withdrawn because of difficulty in obtaining blood samples. The mean ages (SD) for the healthy and asthmatic groups were 31.0 (8.6) and 27.9 (9.6) years, respectively. There were 12 women and 16 men in the healthy group and 8 women and 9 men in the asthmatic group. The two treatment groups were generally comparable, except for BMI values and pulmonary function tests. The healthy group had a mean (SD) body weight of 74.0 (11.4) kg and a mean BMI (SD) of 24.8 (3.1) kg/m^2 . The asthmatic group had a mean (SD) body weight of 79.0 (12.4) kg and a mean BMI (SD) of 28.4 (5.4) kg/m^2 . The mean FEV_1 , FVC, and FEV_1/FVC values for the healthy group were 98, 103, and 97%, respectively. For the asthmatic group, the values for these three parameters were 77, 93, and 83%, respectively. Asthmatic subjects in the study had a mild-to-moderate degree of asthma. The range of FEV_1 while withholding β -agonist for 6 h was 52.5–81%, and the mean

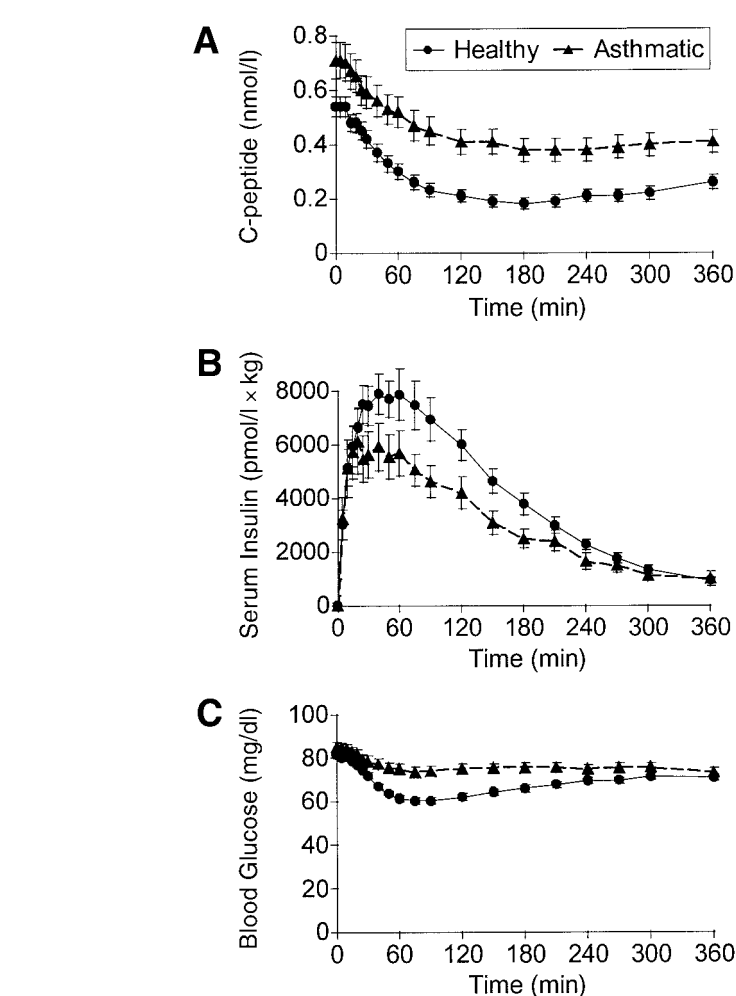


Figure 1—Serum insulin and glucose profiles. Blood samples were taken 0–360 min after inhalation of 1.57 mg of human regular insulin on dosing days 1 and 2. Mean and SE were calculated based on the average of dosing days 1 and 2 for each subject. A: Serum C-peptide concentration over time. B: C-peptide- and body weight-adjusted serum insulin concentration over time. C: Blood glucose concentration over time. Serum insulin concentrations shown in B were adjusted for C-peptide and body weight (see “Statistical methods” for details). ●, healthy; ▲, asthmatic.

reversibility after β -agonist inhalation was 17.9% (range 5.4–123).

PK and PD results.

The mean values for dosing days 1 and 2 at each time point were used to generate insulin and blood glucose profiles. Asthmatic subjects exhibited less insulin absorption after a single inhalation than normal subjects. As shown in Fig. 1A, asthmatic subjects showed consistently higher C-peptide levels than the healthy group at all of the time points, indicating an overall higher level of endogenous insulin secretion. Therefore, the PK parameters [insulin $AUC_{(0-360 \text{ min})}$ and $C_{\max}$] were adjusted for C-peptide levels and baseline body weight (see “Statistical

methods” for details). Asthmatic subjects consistently absorbed less insulin after inhalation, as shown in Fig. 1B. The adjusted mean $AUC_{(0-360 \text{ min})}$ values of insulin were significantly lower for asthmatic subjects than for the healthy group (Table 1). The trend was also generally reflected by lower values for $C_{\max}$. The mean $C_{\max}$ value of the asthmatic group was numerically lower than the healthy group, but the difference was not statistically significant. The median values of insulin $T_{\max}$ for the two groups were comparable and were shorter than what is normally observed from subcutaneous injection.

Consistent with decreased insulin absorption, blood glucose levels in the asth-

Table 1—Summary of PK and PD parameters and intrasubject variability after single inhalation of 45 IU regular human insulin

Parameter	Healthy (n = 28)	Asthmatic (n = 16)	P	Ratio (H/A)	90% CI
Insulin					
Insulin AUC _(0–360 min) (pmol/l × min × kg)	1.45 × 10 ⁶ (7.52 × 10 ⁵)	1.07 × 10 ⁶ (6.39 × 10 ⁵)	0.013*	1.58	1.13–2.21
Insulin C _{max} (pmol/l × kg)	9,872 (5,717)	8,310 (5,398)	0.094	1.25	0.95–1.65
T _{max} (min)	50 (5–120)	45 (10–270)	—	—	—
Glucose					
AOC _(0–360 min) (mg/dl × min)	4,880 (2,199)	3,419 (1,682)	0.007*	1.40	1.12–1.74
C _{min} (mg/dl)	56 (10)	68 (10)	—	—	—
T _{min} (min)	75 (40–360)	83 (30–360)	—	—	—
Intrasubject variability (CV)					
Insulin AUC _(0–360 min)	26.6	47.3	—	—	—
Insulin C _{max}	25.2	48.1	—	—	—
Glucose AOC _(0–360 min)	46.7	40.6	—	—	—
Glucose C _{min}	14.6	11.0	—	—	—

Data are means (SD), median (range), and %. Ratio of geometric means was calculated from log-transformed data. A, asthmatic; H, healthy. Mean values for dosing days 1 and 2 for each subject were used in the analysis. *Indicates significance ($P < 0.05$).

matic group were not reduced to the same extent as they were for the healthy group, as observed by the smaller mean glucose AOC_(0–360 min) of the asthmatic group (Table 1 and Fig. 1C). The two groups had comparable glucose T_{min}, and the C_{min} of the asthmatic group was numerically higher than that of the healthy group (Table 1).

The asthmatic subjects showed greater intrasubject variability for serum insulin AUC_(0–360 min) and C_{max} values than healthy subjects. The intrasubject variability for glucose AOC_(0–360 min) was similar between healthy and asthmatic subjects (Table 1). Asthmatic subjects appeared to show more intrasubject variation in pulmonary insulin absorption than their healthy counterparts.

Pulmonary function

There were no clinically meaningful changes in mean FEV₁, FVC, and FEV₁/FVC values from pre- to postdose times for either group, even at the higher dose (Fig. 2). There were also no reported episodes of airway hyper-reactivity after insulin inhalation in asthmatic subjects. No asthmatic subjects required treatment with inhaled β -agonist following inhaled insulin (subjects were allowed to resume their usual medication 6 h after inhalation). None of the asthmatic subjects had a change in the pattern of their asthma while in the study facility or immediately after discharge.

Safety

All doses of inhaled insulin were well tolerated in both asthmatic and healthy subjects. The most frequently reported adverse events were hypoglycemia, headache, and dizziness. A total of 18 subjects experienced one or more hypoglycemic events. Most hypoglycemic episodes were asymptomatic and were identified by blood glucose readings <50 mg/dl (2.8 mmol/l). The higher insulin dose (4.7 mg, 135 IU) given in part 2 of the study was not associated with an increased incidence of adverse events.

Twenty-one subjects (47%) reported a total of 48 adverse events. The adverse experiences reported were mild, self-limited, and transient. There were no qualitative differences in the incidence of any adverse experience between dosing periods. Single inhalations had no overall effect on blood pressure, heart rate, ECG intervals, laboratory blood parameters, or pulmonary function tests.

CONCLUSIONS— Inhaled insulin has not been previously studied in subjects with chronic asthma. In asthmatic individuals, delivery of inhaled insulin to the blood stream may be affected by the overall efficiency of pulmonary function and airway hyper-reactivity. The purpose of this trial was to determine whether subjects with mild-to-moderate chronic asthma would show any alteration of insulin absorption as compared with

healthy volunteers and to assess the safety of inhaled insulin in asthmatic subjects.

Subjects with asthma have changes in their airway caliber, blood flow, cellular architecture, and changes in airway secretions. These changes are primarily located in their upper airway, whereas insulin is absorbed in the peripheral airway (alveoli). However, the deposition of inhaled aerosols in the lung is somewhat susceptible to airflow obstruction. In the presence of airflow obstruction, the linear flow velocity is increased and there may be turbulent airflow, leading to increased particle deposition in the proximal airways (24). It has been shown that an inhaled aerosol with a particle size of ~ 4 μ m is deposited more peripherally in the airways after bronchodilation in asthmatic subjects (25). Moreover, the differences in the pulmonary vasculature or blood flow in asthmatic subjects might affect the matching of perfusion to ventilation and, hence, the absorption of inhaled insulin from the lung to blood stream.

This study indicates that subjects with chronic asthma absorb less insulin after inhalation than healthy subjects, resulting in a smaller reduction of blood glucose. The decreased insulin absorption in asthmatic subjects might be caused by a difference in the airway caliber, pulmonary vasculature, or blood flow as a result of chronic asthma.

Another possible explanation for reduced blood glucose reduction in asthmatic subjects could be that the asthmatic

subjects were more resistant to insulin than healthy subjects. The asthmatic subjects had a greater mean BMI than the healthy group (24.8 vs. 28.4 kg/m² for healthy and asthmatic subjects, respectively). Obese subjects often exhibit a certain degree of insulin resistance, even without the manifestations of diabetes. A higher degree of insulin resistance in asthmatic subjects was therefore speculated. A post hoc insulin sensitivity analysis (homeostasis model assessment method [HOMA]) (26) revealed that asthmatic subjects were indeed more resistant to insulin than healthy subjects (HOMA indexes were 1.8 and 2.9 for healthy and asthmatic subjects, respectively, $P = 0.005$). Therefore, reduced insulin absorption and increased insulin resistance could both have contributed to less glucose reduction in the asthmatic subjects. Because the sample size was not powered for this test, the results could only be considered supportive evidence.

An interesting observation of this study was that the asthmatic subjects had consistently higher C-peptide levels than healthy volunteers (Fig. 1A). The baseline fasting serum insulin concentrations were 53.1 ± 26.8 pmol/l (mean $\pm$ SD) for the healthy group and 81.3 ± 45.2 pmol/l for the asthmatic group (unadjusted serum insulin profile not shown). Such data indicate a pattern of generally higher endogenous insulin levels in asthmatic subjects. There is a need to distinguish endogenous insulin from exogenous inhaled insulin. Very real differences in serum insulin levels between the two groups could mask possible differences in insulin absorption if no C-peptide adjustment was conducted. It has been reported in the literature that inhaled β_2 -agonists can increase insulin levels in asthmatic subjects (27–29), and thus the observed elevation of C-peptide level may be a direct result of chronic use of asthma medications. It is important to note that inhaled insulin did not exacerbate the baseline airway hyper-reactivity state of asthmatic subjects in this study. No clinically meaningful changes in FEV₁, FVC, and FEV₁/FVC values were observed from pre- to post-dose times, even when insulin was inhaled at a dose approximately three times the dose given in the first two periods. Moreover, no adverse events related to pulmonary function were reported during the dosing periods, and no other safety concerns were noted.

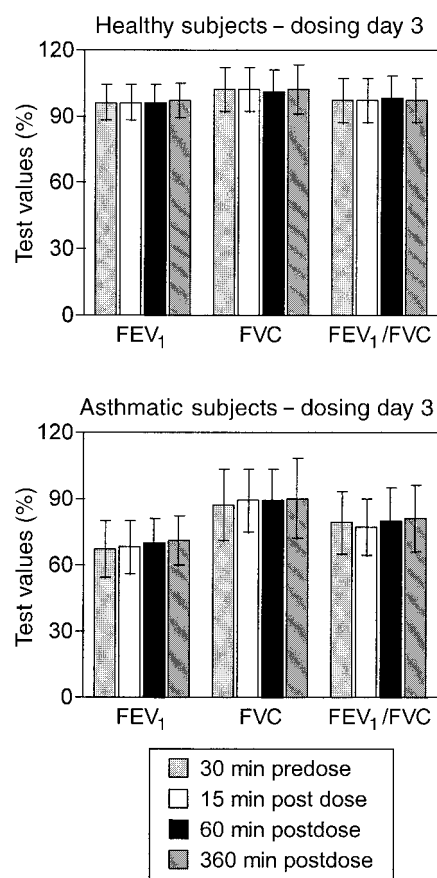


Figure 2—Pulmonary function tests—from pre- to postdose. Pulmonary function tests (FEV₁, FVC, and FEV₁/FVC) were performed on dosing day 3 at 30 min before and 15, 60, and 360 min after inhalation of 4.7 mg of human regular insulin. Test values are shown in percentage of predicted for age, sex, and height. Healthy subjects are shown in the upper panel, and asthmatic subjects are shown in the lower panel. Values are mean (SD).

In conclusion, the results of this study indicate that the AERx iDMS was safe and well tolerated in healthy and in asthmatic but otherwise healthy subjects. No effects on airway reactivity were observed. As compared with subjects without asthma, otherwise healthy asthmatic subjects absorb significantly less insulin and had less reduction of their blood glucose after inhalation of insulin using the AERx iDMS system. On the basis of these results, diabetic patients with asthma may need to inhale more insulin than patients with normal pulmonary function in order to achieve similar glycemic control.

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