The Effect of Smoking Cessation and Subsequent Resumption on Absorption of Inhaled Insulin

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OBJECTIVE — To assess the absorption profile of inhaled insulin in healthy, actively smoking subjects at baseline, after smoking cessation, and after smoking resumption and compare it with nonsmoking subjects.

RESEARCH DESIGN AND METHODS — Insulin pharmacokinetics and glucodynamics were measured in 20 male smoking subjects (10–20 cigarettes/day) and 10 matched nonsmoking subjects after receiving inhaled insulin (1 mg) or the approximate subcutaneous insulin equivalent (3 units) in a randomized cross-over fashion. All smokers then received inhaled insulin 12 h, 3 days, and 7 days into a smoking cessation period. They then resumed smoking for 2–3 days before again receiving inhaled insulin 1 h after the last cigarette.

RESULTS — Before smoking cessation, maximum insulin concentration (C_{max}) and area under the curve (AUC) for insulin concentration time (AUC-Insulin$_{0-360}$) with inhaled insulin were higher, and time to C_{max} (t_{max}) shorter, in smokers than nonsmokers (C_{max} 26.8 vs. 9.7 μU/ml; AUC-Insulin$_{0-360}$ 2,583 vs. 1,645 $\mu U \cdot ml^{-1} \cdot min^{-1}$; t_{max} 20 vs. 53 min, respectively; all $P < 0.05$), whereas with subcutaneous insulin, systemic exposure was unchanged (AUC-Insulin$_{0-360}$ 2,324 vs. 2,269 $\mu U \cdot ml^{-1} \cdot min^{-1}$; P = NS). After smoking cessation, AUC-Insulin$_{0-360}$ decreased with inhaled insulin by up to 50% within 1 week and approached nonsmoker levels. C_{max} decreased and t_{max} increased relative to baseline but were still not comparable with nonsmoker values. Smoking resumption completely reversed the effect of smoking cessation. Glucodynamics corroborated the observed findings in insulin pharmacokinetics.

CONCLUSIONS — Cessation and resumption of smoking greatly altered the pharmacokinetics of inhaled insulin. As rapid changes in systemic insulin exposure increase hypoglycemia risk, inhaled insulin should not be used in people with diabetes who choose to continue smoking. This is consistent with recommendations that people with diabetes refrain from smoking altogether.

Diabetes Care 29:277–282, 2006

Inhaled insulin is being developed as an alternative method of insulin administration. It has a faster onset of action than either regular human insulin or insulin lispro injected subcutaneously but retains a duration of action that is longer than that of short-acting analogs of human insulin (1). These characteristics suggest that inhaled insulin is suitable for prandial insulin supplementation in patients with diabetes. Accordingly, the results of large-scale clinical trials show that inhaled insulin is effective and well tolerated in patients with type 1 and type 2 diabetes and that it may prove to be a novel and well-accepted component of diabetes therapy for many patients (2–5). In long-term extension trials, >80% of insulin-treated patients preferred an inhaled insulin regimen over standard subcutaneous insulin therapy (6). Furthermore, the availability of inhaled insulin could, in theory, help to overcome patient aversion to insulin therapy in general (7).

Pulmonary permeability determines the absorption of inhaled peptides, and smoking has been shown to increase the permeability of the lungs to diethylenetriamine penta-acetic acid radioaerosols (8–11), an effect that is independent of the presence of nicotine in the blood (12). Accordingly, smoking has been shown specifically to increase inhaled insulin absorption in healthy volunteers (13–16). Therefore, the nicotine-independent effects of tobacco smoke on the lung may have implications for inhaled insulin therapy.

In smokers, cessation of smoking significantly decreases the clearance of radioaerosol particles from the lung and decreases permeability within 1–3 weeks; however, complete reversal of the increased permeability in smoking relative to nonsmoking subjects is not achieved within that period (9,17). Nevertheless, a significant impact on alveolar permeability can be observed after only 12–24 h without smoking (17,18). Recent studies with inhaled insulins show that 3–4 weeks of smoking cessation restores inhaled insulin absorption kinetics and glucodynamic responses toward those of healthy nonsmoking volunteers (15,19), an effect that does not change further after 3 months of smoking cessation (15). However, the time course of the onset and offset of the effects of smoking cessation and resumption on inhaled insulin absorption is currently not known. The purpose of this study was *1*) to investigate the absorption profile of inhaled insulin (Exubera) in healthy nondiabetic active chronic smokers at baseline, after smoking cessation, and after smoking resumption, and *2*) to compare inhaled insulin absorption in smokers with that in healthy nonsmokers.

RESEARCH DESIGN AND METHODS

— This study was carried out according to the principles of the Declaration of Helsinki and Good Clinical

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Received for publication 7 October 2005 and accepted in revised form 11 November 2005.

Abbreviations: AUC, area under the curve.

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

Practice and in keeping with local legal and regulatory requirements in Germany. It was approved by the local ethics committee.

This single-center, open-label study included two study groups: *1*) 20 active chronic smokers willing to quit smoking for 7 days and then resume again and *2*) 10 matched nonsmokers. Inclusion criteria included a normal oral glucose tolerance test, predose fasting blood glucose ≥80 mg/dl, and HbA_{1c} <6.4%. In addition, the lung function parameters of forced expiratory volume in 1 s and forced vital capacity had to be >75% of predicted values. All subjects provided written informed consent.

The study consisted of three parts. In the first part, all subjects (smokers and nonsmokers) received a single 1-mg dose of inhaled insulin and a single 3-unit dose of subcutaneous regular human insulin, separated by at least 6 days, in a randomized cross-over fashion. This established the inhaled insulin baseline pharmacokinetics/glucodynamics for smokers ($INH1_{Sm}$) and nonsmokers ($INH1_{NSm}$) and was the only part in which nonsmokers participated. All smokers then proceeded to part 2 of the study, which consisted of three sequential treatment stages where a single dose of inhaled insulin was administered on day 1 ($INH2_{Sm}$, 12 h after smoking cessation), day 3 ($INH3_{Sm}$, 3 days after smoking cessation), and day 7 ($INH4_{Sm}$, 7 days after smoking cessation). During these 7 days, subjects were not allowed to smoke until the final blood sample was taken on day 7. In part 3, subjects resumed smoking (20 cigarettes/day) until receiving a single dose of inhaled insulin on either day 9 or 10 ($INH5_{Sm}$, 2 or 3 days after resumption of smoking). For parts 1 and 3, smokers had their last cigarette 1 h before, and did not resume smoking until 3 h after, the administration of study medication. For part 2, smokers had their last cigarette 12 h before $INH2_{Sm}$ and then ceased smoking until 6 hours after $INH4_{Sm}$. All smokers were hospitalized for the duration of parts 2 and 3 of the study.

Regular human insulin (HOE31 HPR 100; Aventis Pharma Deutschland, Frankfurt, Germany) was administered by subcutaneous injection into a lifted abdominal skinfold by a health care professional using a disposable syringe (MicroFine 0.3 ml 28G 1/2; Becton Dickinson, Franklin Lakes, NJ). Inhaled insulin (1 mg Exubera) was administered as an aerosolized cloud from the holding chamber (volume 240 ml) of the Exubera Pulmonary Delivery System (Nektar Therapeutics, San Carlos, CA); 1 mg Exubera contains 27.5 units human insulin. Subjects were instructed to inhale steadily and deeply after a normal exhalation and to hold their breath for 5 s afterward.

Pharmacokinetic and glucodynamic evaluations

An intravenous cannula was inserted into the forearm to collect blood samples for determination of blood glucose, immunoreactive serum insulin, plasma carboxyhemoglobin, and serum cotinine. Samples (sufficient to provide 2 ml serum) for glucose, insulin, and C-peptide measurement were taken 60, 30, and 15 min before insulin dosing and predose, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300, and 360 min after administration. Samples for carboxyhemoglobin (1 ml of EDTA whole blood) and cotinine (2 ml blood for 1 ml serum) were taken 60 min before study medication on all dosing days. Immunoreactive serum insulin and serum C-peptide were determined by radioimmunoassays (Prof. Hans K.L. Hundt, FARMOVS-PAREXEL, Bloemfontein, South Africa). A rat insulin radioimmunoassay kit from Linco Research (St. Charles, MO) was used along with a human insulin calibration standard and quality control samples prepared by FARMOVS-PAREXEL. The C-peptide kit (C-PEP-RIA CT) was supplied by BioSource Europe (Nivelles, Belgium). Blood glucose was determined by glucometer (GlucoTouch; Lifescan, Milpitas, CA).

Statistical methods

For pharmacokinetic analysis, area under the curve (AUC) for serum insulin concentration time between 0 and 360 min ($AUC\text{-}Insulin_{0-360}$; calculated by the linear trapezoidal rule), maximum concentration (C_{max}), and time to C_{max} (t_{max}) were determined for each subject and insulin administration. Exogenous insulin concentrations were derived using C-peptide correction. Statistical comparisons among smokers over time (i.e., $INH1_{Sm}$ and $INH2\text{–}5_{Sm}$) used the paired Student's *t* test on ln(AUC) and ln(C_{max}) (i.e., natural log-transformed data); untransformed t_{max} was analyzed using the Wilcoxon's signed-rank test. For the comparison of smokers versus nonsmokers in part 1 (i.e., $INH1_{Sm}$ versus $INH1_{NSm}$ and subcutaneous $[SC]_{Sm}$ versus SC_{NSm}), an ANOVA model with group effects was used to analyze ln(AUC) and ln(C_{max}); t_{max} was analyzed by nonparametric analysis. For the comparison of inhaled and subcutaneous insulin in part 1 of the study (i.e., $INH1_{Sm}$ versus SC_{Sm} and $INH1_{NSm}$ versus SC_{NSm}), an ANOVA model with subject, treatment, and period effects was used to analyze ln(AUC) and ln(C_{max}); t_{max} was analyzed by nonparametric analysis. For the mean ratios of all pairwise group comparisons for AUC and C_{max}, 90% CIs were calculated; for t_{max}, nominal 90% nonparametric CIs for the respective median difference in groups were calculated based on the Hodges-Lehmann estimator. Relative bioavailability was calculated as the ratio of the dose-adjusted AUCs (between 0 and 360 min) for inhaled and subcutaneous insulin (i.e., $(AUC_{INH}/Dose_{INH})/(AUC_{SC}/Dose_{SC})$).

For glucodynamic analysis, AUC for change in blood glucose concentration ($AUC\text{-}GLU_{0-360}$), maximum change in blood glucose (ΔGLU_{max}), and time to ΔGLU_{max} ($t\Delta_{GLUmax}$) were calculated to compare the extent of blood glucose excursions. Statistical comparisons were identical to those used for pharmacokinetic data.

RESULTS — Twenty otherwise healthy nondiabetic male smokers (mean age 28.4 years [range 21–44], BMI 22.4 kg/m^2 [20–26]) and 10 matched nonsmokers (mean age 28.2 years [19–37], BMI 24.5 kg/m^2 [19–28]) participated in this study. Smokers had been smoking 10–20 cigarettes per day (mean 16.4) for an average of 11.4 years (range 2–28). Smoking status and adherence to smoking protocols was confirmed by a carboxyhemoglobin level >1.9% and serum cotinine concentrations >100 ng/ml at screening and during the randomized two-way crossover baseline study (Table 1). The nonsmoking group consisted of four ex-smokers (no smoking for ≥8 months) and six subjects who had never smoked. Nonsmoking status was confirmed by a carboxyhemoglobin level <1.2% and serum cotinine concentrations below the detection limit of 10 ng/ml in nonsmokers.

Randomized two-way crossover baseline (part 1)

Systemic insulin exposure ($AUC\text{-}Insulin_{0-360}$) with inhaled insulin was significantly higher in smokers compared with nonsmokers (INH_{Sm}/INH_{NSm} = 1.57) (Table 2, Fig. 1*A*). Systemic insulin exposure after subcutaneous insulin, on

Table 1—*Smoking status at screening and prior to study visits, as indicated by serum cotinine and plasma carboxyhemoglobin levels*

	Serum cotinine level (ng/ml)	Carboxyhemoglobin (%)
Nonsmokers (n = 10)		
Screening	<10 (<10)	0.6 (0.4–1.1)
Cross-over visit 1	<10 (<10)	0.2 (0.2–0.8)
Cross-over visit 2	<10 (<10–15)	0.2 (0.2–1.2)
Smokers (n = 20)		
Screening	303 (120–466)	4.8 (2.7–9.2)
Cross-over visit 1	297 (149–522)	3.8 (1.9–15.2)
Cross-over visit 2	282 (184–489)	3.9 (2.2–6.6)
$INH2_{Sm}$ visit	276 (124–494)	2.3 (1.6–3.9)
$INH3_{Sm}$ visit	<29 (<10–71)	0.8 (0.4–2.9)
$INH4_{Sm}$ visit	<10 (<10–13)	0.5 (0.9–1.4)
$INH5_{Sm}$ visit	243 (114–402)	2.7 (1.6–3.8)

Data are median (range).

the other hand, was not significantly different (SC_{Sm}/SC_{NSm} = 0.98). Maximum insulin concentration (C_{max}) after inhaled insulin was about three times higher in smokers (INH_{Sm}/INH_{NSm} = 2.77), whereas C_{max} after subcutaneous insulin was not significantly different in smokers (SC_{Sm}/SC_{NSm} = 1.17). Time to t_{max} after inhaled insulin was significantly shorter in smokers than in nonsmokers (median 20.0 vs. 52.5 min), whereas after subcutaneous insulin, t_{max} was not significantly different (median 90 min in both cases).

Smoking cessation and resumption (parts 2 and 3)

Twelve hours after smoking ceased ($INH2_{Sm}$), total systemic insulin exposure with inhaled insulin was significantly increased compared with baseline ($INH2_{Sm}/INH1_{Sm}$ = 1.22). C_{max} was also increased ($INH2_{Sm}/INH1_{Sm}$ = 1.22), whereas t_{max} remained unchanged at 20.0 min (Table 2, Fig. 1*B*). However, after 3 days of smoking cessation ($INH3_{Sm}$), total systemic insulin exposure had started to decline relative to baseline ($INH3_{Sm}/INH1_{Sm}$ = 0.90), C_{max} was significantly lower ($INH3_{Sm}/INH1_{Sm}$ = 0.69), and t_{max} was significantly longer (median 30.0 min). After 7 days of smoking cessation ($INH4_{Sm}$), the decrease in total systemic insulin exposure had become significant relative to baseline ($INH4_{Sm}/INH1_{Sm}$ = 0.73), such that it became comparable with nonsmokers ($INH1_{NSm}/INH4_{Sm}$ = 0.87). C_{max} was reduced further ($INH4_{Sm}/INH1_{Sm}$ = 0.59) and t_{max} delayed further (median 37.5 min). These values approached those of nonsmokers, such that the difference in t_{max} relative to nonsmokers became nominal, although C_{max} was still significantly higher ($INH1_{NSm}/INH4_{Sm}$ = 0.61). Resumption of smoking for 2–3 days ($INH5_{Sm}$) restored total systemic insulin exposure ($INH5_{Sm}/INH1_{Sm}$ = 1.22) and C_{max} ($INH5_{Sm}/INH1_{Sm}$ = 1.09) to the smoker baseline, although t_{max} remained significantly delayed at 30.0 min.

Adherence to smoking cessation was confirmed by carboxyhemoglobin levels, which declined rapidly within 12 h to half of the >1.9% baseline level and to nonsmoking levels within 3 days of smoking cessation (Table 1). Serum cotinine concentrations remained almost unchanged 12 h after cessation of smoking (in line with the approximate 24-h half-life of nic-

Table 2—*Pharmacokinetic summary measures (C-peptide corrected) after inhalation of 1 mg insulin or subcutaneous injection of 3 units regular human insulin in nondiabetic nonsmokers and smokers at baseline, after smoking cessation, and after smoking resumption*

	$AUC\text{-}Insulin_{0–360}$ ($\mu U \cdot ml^{-1} \cdot min^{-1}$)*	C_{max} (μU/ml)*	t_{max} (min)†
SC_{NSm}	2,324	11.6	90.0 (127.5)
SC_{Sm}	2,269	13.6	90.0 (97.5)
$INH1_{NSm}$	1,645	9.7	52.5 (55.0)
$INH1_{Sm}$	2,583	26.8	20.0 (21.8)
$INH2_{Sm}$	3,165	33.3	20.0 (22.5)
$INH3_{Sm}$	2,321	18.5	30.0 (37.8)
$INH4_{Sm}$	1,887	15.8	37.5 (41.8)
$INH5_{Sm}$	3,156	29.2	30.0 (30.3)
	Mean AUC ratio (90% CI)	Mean C_{max} ratio (90% CI)	t_{max} median difference (90% CI)
SC_{Sm}/SC_{NSm}	0.98 (0.82–1.16); P = NS	1.17 (0.94–1.45); P = NS	−15.0 (−60.0 to 15.0); P = NS
$INH1_{Sm}/INH1_{NSm}$	1.57 (1.15–2.14); $P < 0.05$	2.77 (1.99–3.85); $P < 0.001$	−30.0 (−55.0 to −10.0); $P < 0.01$
$INH1_{NSm}/SC_{NSm}$	0.71 (0.52–0.97); P = NS	0.83 (0.64–1.08); P = NS	−57.5 (−135.0 to −15.0); $P < 0.05$
$INH1_{Sm}/SC_{Sm}$	1.14 (0.96–1.35); P = NS	1.97 (1.60–2.42); $P < 0.001$	−70.0 (−80.0 to −55.0); $P < 0.001$
$INH2_{Sm}/INH1_{Sm}$	1.22 (1.04–1.45); $P < 0.05$	1.24 (1.06–1.46); $P < 0.05$	2.5 (−5.0 to 10.0); P = NS
$INH3_{Sm}/INH1_{Sm}$	0.90 (0.74–1.08); P = NS	0.69 (0.58–0.82); $P < 0.01$	10.0 (10.0–25.0); $P < 0.001$
$INH4_{Sm}/INH1_{Sm}$	0.73 (0.60–0.88); $P < 0.05$	0.59 (0.50–0.69); $P < 0.001$	17.5 (10.0–30.0); $P < 0.01$
$INH5_{Sm}/INH1_{Sm}$	1.22 (1.03–1.45); P = NS	1.09 (0.91–1.31); P = NS	10.0 (0.0–15.0); $P < 0.01$
$INH1_{NSm}/INH4_{Sm}$	0.87 (0.62–1.22); P = NS	0.61 (0.47–0.80); $P < 0.01$	15.0 (−10.0–30.0); P = NS

$AUC\text{-}Insulin_{0–360}$ = area under the serum insulin concentration versus time curve between 0 and 360 min. *Geometric mean values; †Median (arithmetic mean) values.

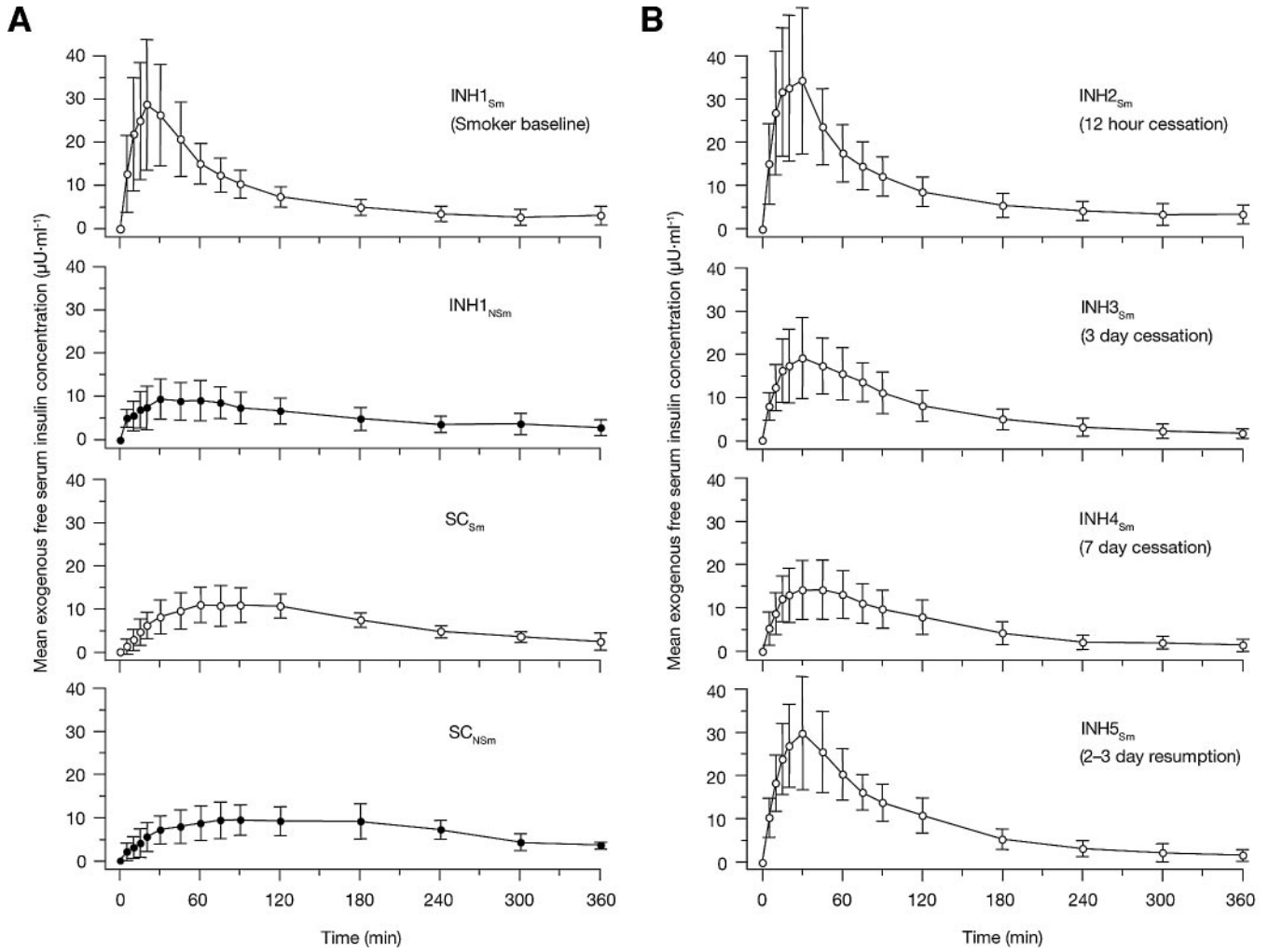

Figure 1—*Serum insulin concentration time profiles after inhalation of 1 mg insulin (INH) or subcutaneous injection of 3 units regular human insulin (SC) in nondiabetic smokers (Sm;* n = *20) and nonsmokers (NSm;* n = *10).* A*: Baseline cross-over study.* B*: After smoking cessation (*$INH2_{Sm}$*-*$INH4_{Sm}$*) and resumption (*$INH5_{Sm}$*). Data are means ± SD.*

otine in blood) and decreased thereafter from >100 ng/ml at baseline to near nonsmoking concentrations within 3 days (Table 1). Resumption of smoking caused restoration to baseline concentrations.

Relative bioavailability

Bioavailability, as determined from the AUC-$Insulin_{0-360}$, of inhaled insulin relative to subcutaneous insulin at baseline was 8% in nonsmokers and 12% in smokers. Short-term (12-h) cessation of smoking increased the bioavailability to 15% in smokers. However, longer cessation of smoking progressively reduced bioavailability to 11% after 3 days and to 9% after 1 week, approaching the bioavailability of 8% in nonsmokers. Resumption of smoking for 2–3 days restored the bioavailability back to the smoker level of 15%.

Glucodynamic results

The glucodynamic results were consistent with those seen for pharmacokinetics. The glucodynamic response to inhaled insulin was much greater in smokers than in nonsmokers ($INH1_{Sm}$/$INH1_{NSm}$–to–AUC-GLU_{0-360} ratio = 1.73, $P < 0.05$; $INH1_{Sm}$/$INH1_{NSm}$–to–ΔGLU_{max} ratio = 2.74, $P < 0.001$) and $t_{\Delta GLUmax}$ was nominally shorter in smokers, which approached significance (median 45 vs. 75 min). Subcutaneous insulin, on the other hand, was equivalent in smokers and nonsmokers (SC_{Sm}/SC_{NSm}–to–AUC-GLU_{0-360} ratio = 1.22; SC_{Sm}/SC_{NSm}–to–ΔGLU_{max} ratio = 1.30; median $t_{\Delta GLUmax}$ = 120 vs. 180 min). After smoking cessation for 12 h, the glucodynamic response with inhaled insulin was not significantly altered relative to baseline smoker levels, although it nominally increased ($INH2_{Sm}$/$INH1_{Sm}$–to–AUC-GLU_{0-360} ratio = 1.16; $INH1_{Sm}$/$INH1_{NSm}$–to–ΔGLU_{max} ratio = 1.19) with unchanged median $t_{\Delta GLUmax}$ at 53 min. The response declined after cessation for 3 days and was about equivalent to that in nonsmokers after 1 week ($INH4_{Sm}$/$INH1_{Sm}$–to–AUC-GLU_{0-360} ratio = 0.74; $INH1_{Sm}$/$INH1_{NSm}$–to–ΔGLU_{max} ratio = 0.49) with median $t_{\Delta GLUmax}$ delayed to 82.5 min. The glucodynamic response was restored to baseline after resumption of smoking for 2–3 days ($INH4_{Sm}$/$INH1_{Sm}$–to–AUC-GLU_{0-360} ratio = 0.87; $INH1_{Sm}$/$INH1_{NSm}$–to–ΔGLU_{max} ratio = 0.82) with median $t_{\Delta GLUmax}$ down to 56 min.

Safety and tolerability

A total of four treatment-related adverse events were reported in two subjects during the study (two moderate hypoglyce-

mia, one mild headache, and one moderate asthenia); all were in the smoker group. Both cases of hypoglycemia occurred with inhaled insulin ~1 h after $INH2_{Sm}$, and no action was required. No subject was discontinued or had a dose reduction owing to adverse events. Spirometry tests revealed no clinically relevant changes in either group. There were no clinically relevant changes in vital signs in either group, and physical examinations also showed no treatment-related changes.

CONCLUSIONS — The results from this study are consistent with previous reports that the absorption of inhaled insulin and other small molecules is increased in smokers compared with nonsmokers (8–11,13–16). They are also consistent with a preliminary report showing that smoking cessation for 3 weeks reduced inhaled insulin absorption by ~50% toward the levels seen in nonsmokers, an effect that was not reduced further after 3 months' smoking cessation (15). However, this is the first study to describe the early time course of the onset of smoking cessation effects on inhaled insulin absorption and reveals that smoking cessation for only 1 week decreases total pulmonary absorption to almost that of healthy nonsmoker levels. However, in spite of this, the other inhaled insulin pharmacokinetic parameters (C_{max} and t_{max}) indicate that the apparent rate of absorption remains altered to some extent after a week of smoking cessation. This is also the first study to show that resumption of smoking restores the changes that occurred during smoking cessation back to the levels seen in chronic smokers after only 2–3 days. This restoration may start to occur very rapidly upon resumption of smoking; preliminary evidence from a recent study reveals a tendency for pharmacokinetic and glucodynamic parameters to revert to precessation levels <90 min after resumption of smoking (19).

The pharmacokinetic profile of inhaled insulin reported here is consistent with previous reports for this and other formulations (1,25). In a glucose-clamp study, Rave et al. (1) reported a t_{max} of 55 min using Exubera inhaled insulin, identical to that shown here. Furthermore, the bioavailability of inhaled insulin relative to subcutaneous regular human insulin in our study was 8% in nonsmokers, which compares well with the 9% reported previously (1).

The study by Himmelman et al. (16) used a different insulin inhalation system that utilizes a liquid aerosol formulation, as opposed to the dry-powder formulation in the present study, and also showed a higher AUC-$Insulin_{0–360}$ and C_{max} and a shorter t_{max} for inhaled insulin in smoking subjects. Thus, the effects of smoking on inhaled insulin absorption are not formulation specific. Rather, they reflect a general increase in airway epithelial permeability associated with smoking, consistent with predictions from radioaerosol lung clearance (8–11). In fact, the time course observed in our study closely mirrors that observed for radioaerosols with smoking cessation and resumption (9,18). For perspective, acute passive exposure to tobacco smoke, in contrast to active smoking, is expected not to alter (or at most to reduce to a small extent) absorption of inhaled insulin based on studies with diethylenetriamine penta-acetic acid (26). The exact mechanism underlying the increased airway permeability with smoking is not yet fully understood, although it is nicotine-independent (12) and may be associated with increased oxidative stress (18).

In a previous study, smokers had a higher incidence of hypoglycemia after inhaled insulin administration, reflecting the enhanced rate and extent of absorption of inhaled insulin in smokers (15). In the present study, there were two incidences of hypoglycemia, both of which occurred in the smoker group with inhaled insulin administration 12 h after smoking cessation. It is interesting to note that this is the point at which a transient increase in insulin exposure occurred, such that bioavailability increased from 12 to 15%. Whether this transient increase is real or artifactual remains undetermined. However, although not designed to investigate the time course of smoking cessation, the study by Himmelman et al. (16) appears to show a compatible effect. Inhaled insulin absorption was increased to a greater degree (relative to nonsmoking subjects) when smoking subjects completely abstained from smoking overnight compared with when they smoked acutely during the 30 min before inhaled insulin administration. Thus, it appears that smoking may also have acute inhibitory effects on airway permeability that are masked by the chronic effects of increased permeability, and produce a rapid and transient rebound in permeability during the 1st day of smoking cessation.

Diabetes health organizations unanimously recommend that people with diabetes should not start or continue to smoke, as smoking substantially increases the risk of developing cardiovascular disease and diabetes complications, especially neuropathy and nephropathy (20–23). The precise metabolic effects of nicotine in people with diabetes are yet to be firmly established, although some evidence suggests that nicotine increases insulin resistance and has adverse effects on glucose homeostasis (21,24). Unfortunately, the prevalence of smoking among individuals with diabetes remains comparable with the general population (20). The results of the present study confirm that patients are required to abstain from smoking before starting and when continuing treatment with inhaled insulin.

In summary, this study shows that *1*) inhaled insulin absorption is increased in smokers compared with nonsmokers, consistent with previous studies; *2*) the effect of smoking on insulin absorption is reversed after only 1 week of smoking cessation, although the absorption profile remains altered relative to that of nonsmokers; *3*) changes in absorption occur rapidly after only 12 h of smoking cessation and may involve a transient increase in absorption; and *4*) the insulin absorption profile rapidly reverts back to that seen in chronic smokers after only 1–2 days of smoking resumption. We therefore conclude that, as short-term changes in insulin availability may increase hypoglycemia risk, people with diabetes who smoke must quit smoking before commencing treatment with inhaled insulin and that inhaled insulin should not be used in those who choose to continue smoking. This conclusion is consistent with recommendations that people with diabetes should refrain from smoking altogether (20–23).

Acknowledgments — This study was presented at the Scientific Sessions of the American Diabetes Association, New Orleans, Louisiana, 13–19 June 2003, and the Congress of the International Diabetes Federation, 24–29 August 2003. It was supported by Pfizer (New York, NY) and Aventis, a member of the sanofi-aventis Group (Bridgewater, NJ), who are developing Exubera with Nektar Therapeutics (San Carlos, CA).

Richard Piechatzek and colleagues conducted the study at the Görlitz clinical unit of IMFORM, Darmstadt, Germany.

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