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Diabetic Medicine
Volume 21 Page 763 - July 2004
doi:10.1111/j.1464-5491.2004.01240.x
Volume 21 Issue 7

Inhaled micronized crystalline human insulin using a dry powder inhaler: dose-response and time-action profiles¹

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Diabetic Medicine

Journal of Diabetes UK



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Abstract

Aim The aim of this euglycaemic glucose clamp study was to investigate the pharmacokinetics, glucodynamics, safety and tolerability of micronized crystalline human insulin inhalation powder delivered by a Spiros® dry powder inhaler system in healthy volunteers.

Methods Thirteen healthy, non-smoking, male and female volunteers [age 30 ± 7 years; BMI 23.5 ± 2.7 kg/m²; (mean $\pm$ sd)] with normal pulmonary function participated in an open-label, randomised, 6-period crossover trial. Each volunteer received four single doses of inhaled insulin (60, 90, 120, 150 U) on separate occasions. For comparison, each volunteer also received two of three possible doses of subcutaneous (s.c.) injected regular human insulin (8, 14, or 20 U).

Results Serum immunoreactive insulin following inhalation of insulin peaked an average of 60 min earlier compared with s.c. injected insulin ($P < 0.0001$). Following inhalation, the time to maximum glucose infusion rate occurred an average of 70 min earlier than with s.c. insulin: 187, 129, 161 and 162 min vs. 227, 241 and 241 min ($P < 0.0001$). The dose-response relationships for serum insulin pharmacokinetics and glucodynamics were linear for both inhaled and s.c. insulin. Relative bioavailability (based on serum insulin levels) ranged from 11.5 to 12.2% for the four doses of inhaled insulin and relative biopotency (based on glucose infusion rates) was 10.0 to 16.5%, respectively. Dosing was well tolerated by all volunteers.

Conclusion This study demonstrates that inhalation of human insulin via a dry powder inhaler system provides a promising alternative route for administration of insulin.

Diabet. Med. (2004)

Introduction

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The lung is an attractive site for insulin delivery because it presents a large surface area and a thin epithelial barrier that facilitates absorption [1]. Delivery of insulin via the lung was first attempted in the 1920s [2,3], however, the development of practical and reliable aerosol systems required that numerous technical barriers be overcome. The increasing prevalence of Type 2 diabetes mellitus (DM) combined with patients' desire for non-invasive insulin delivery methods has sparked new interest in addressing these challenges. Currently, several alternative insulin delivery systems are in various stages of development [2,3].

A number of experimental clinical trials have provided proof of concept for administering insulin via the pulmonary system with acceptable safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) results [4–6]. Glucose clamp studies in healthy volunteers have established clear dose-response relationships for inhaled insulin, and have shown shorter times to peak serum insulin concentration and maximum glucose infusion rate when compared with subcutaneous (s.c.) injection of regular human insulin [6,7].

More recently, the feasibility of inhaled insulin for treatment of patients with Type 1 and Type 2 DM has been examined. Findings from these studies suggest that pulmonary insulin therapy may be particularly well suited to supply meal-time insulin [8,9]. However, the optimal technology to administer insulin to the lung remains to be established. Liquid and dry powder formulations of inhaled insulin along with several types of delivery devices are currently being evaluated [7–9].

The purpose of this study was to investigate the dose-response and dose-equivalency of a unique micronized crystalline inhaled insulin delivered by a dry powder inhaler (DPI), as assessed by pharmacokinetic and glucodynamic variables when compared with s.c. regular human insulin. In addition, safety and tolerability and intra- and inter-subject variability of inhaled insulin (inh) were assessed in a cohort of healthy volunteers.

☐ D. Muchmore

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Keywords

☐ dose-response

☐ glucose-clamp

☐ inhaled insulin

☐ pharmacokinetic

☐ time-action

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Accepted 30 September 2003

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¹Previously published abstract

Rave K, Muchmore D, Gonzales C, Chien JY, Ernest CS, Nosek L, Heinemann L. Inhaled insulin with an improved Spiros® dry powder inhaler: Dose-response and time-action profiles. *Diabetologia* 2001; **44**: (Suppl. 1): A211.

Abbreviations

AUC_{INS} area-under-the-serum-insulin-time-curve

BMI body mass index

Materials and methods

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Volunteers

Thirteen healthy, non-smoking male and female volunteers (without diabetes) between the ages of 22 and 42 participated in this study. Volunteers were required to have a body mass index (BMI) of $\leq 27\text{ kg/m}^2$ and normal (greater than 75% predicted) pulmonary function tests (1-s forced expiratory volume [FEV₁] and forced vital capacity [FVC]) based on their age, sex, height, weight and ethnic origin). Exclusion criteria included a history of impaired glucose tolerance, presence of hoarseness, cough, asthma, or other acute or chronic pulmonary ailments.

Design

This euglycaemic glucose clamp study utilized an open-label, randomised, 6-period crossover design and was conducted at one study centre (Profil Institute for Metabolic Research, Neuss, Germany). The protocol was reviewed and approved by a local Ethics Committee. All procedures were conducted in a manner consistent with the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline to Good Clinical Practice. Written informed consent was obtained from all participants.

An incomplete block design was chosen in order to have sufficient data to assess adequately dose-response and account for the possibility of discontinuations due to the prolonged duration of the study. Power calculations indicated that only nine subjects completing all six treatment periods were needed to provide 90% power to detect a statistically significant linear relationship between dose of inhaled insulin and total amount of glucose infused (GIR_{tot}). These calculations were based on a previous study that had employed a developmental version of the inhaled insulin system used in the present study [10].

Dosage and administration

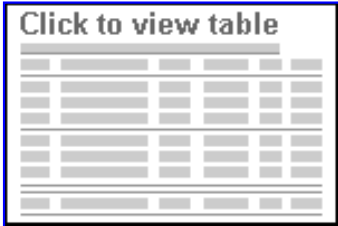
Each volunteer received four doses of pulmonary insulin and two doses of s.c. insulin on different visits separated by a minimum of 5 days. Pulmonary doses were administered as 2, 3, 4 or 5 separate and consecutive oral inhalations per dose which corresponded to 60, 90, 120 and 150 U of human insulin powder for inhalation (HIIP). For comparison, each volunteer received two of three possible doses of s.c. injected regular human insulin, i.e. 8, 14 or 20 U.

HIIP delivery system consisted of a Spiros® blisterdisk dry powder inhaler and HIIP blisterdisks. HIIP was a preparation of 11% micronized insulin crystals blended with the carrier lactose monohydrate NF (National Formulary). The blend was filled into blisterdisks at a target fill weight of 9.5 mg per blisterwell, resulting in 1.05 mg of insulin (30 U) in each blisterwell. The median aerodynamic particle size of the micronized insulin crystals was 2–3 μm , and the median size of the lactose particles was 150 μm .

The hand-held inhaler was a breath-actuated device (Dura Pharmaceuticals Aerosol Research Laboratories, San Diego, CA, USA and Eli Lilly and Company) that delivered HIIP to the subject upon inhalation (Fig. 1). The patient's inspiratory flow activated a battery-powered, twin-blade impeller that assisted in de-agglomeration of the drug and carrier during the inspiration [11]. In detail, when the button of the inhaler was pressed, one blisterwell of the blisterdisk opened, causing the powder within to empty into the dump chamber. A pressure tap in the mouthpiece provided vacuum to a switch, causing the motor-driven impeller to rotate during inhalation. Air passed into and through the dump chamber, fluidizing the powder and moving it down the air/powder path to the impeller chamber. Once in the chamber, the impeller impacted the formulation to efficiently disperse the contents. The substance then passed through the mouthpiece restrictor plate holes and out through the mouthpiece to the patient. The powder/air contact regions were designed to provide consistent aerosol performance across a range of flow rates.

- C_{max}maximum serum insulin concentration
- DMdiabetes mellitus
- DPIdry powder inhaler
- FEV₁forced expiratory volume
- FVCforced vital capacity
- GIRglucose infusion rate
- GIR_{max}maximal glucose infusion rate
- GIR_{tot}total amount of glucose infused
- GIR T_{max}time to maximal infusion rate
- HIIPhuman insulin powder for inhalation
- inhinhaled insulin
- IRIimmunoreactive insulin
- NFNational Formulary
- PDpharmacodynamics
- PKpharmacokinetics
- s.c.subcutaneous
- T_{max}tune of maximum serum insulin concentration

Image Previews



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Table 1 Pharmacokinetic and glucodynamic summary measures for inhaled and s.c. regular human insulin

All volunteers were trained on the proper use of the Spiros® inhaler system. Training was followed by observation of the volunteer's inspiratory performance using a computerized inhalation training system. Volunteers were trained to achieve a consistent inhalation flow rate of 20 l/min through the inhaler (one breath per unit dose) and instructed to inhale for 5 s per inhalation manoeuvre, followed by a 5-s breathhold period. The required number of inhalations per dose was completed in a total of 6 min.

The comparator drug was regular human insulin (Humulin® R supplied in 10-ml vials, 100 U/ml). All s.c. injections 8, 14 or 20 U of regular human insulin were given at a 90° angle into the lifted skin fold of the left abdominal wall, on a line between the umbilicus and the anterior superior iliac spine (50–100 mm lateral of the umbilicus) by means of a syringe (Microfine IV+, Becton-Dickinson, Heidelberg, Germany). This procedure ensured strict s. c. injection of the insulin preparation.

Glucose clamp procedure

Subjects were prepared for the glucose clamps by an overnight fast of 10–12 h. The glucose clamp procedure was conducted using the Biostator (glucose-controlled insulin infusion system—GCIIS, Life Science Instruments, Elkhart, IN, USA) to regulate glucose infusion rates in response to the changes of blood glucose levels. After connection with the Biostator, baseline blood glucose level of volunteers was registered over a 90-min period prior to dosing. At the end of this baseline period, insulin was administered by inhalation or s.c. injection and glucose infusion rates were registered for the subsequent 10 h. After administration of insulin, blood glucose was clamped at a level 5% below the individual mean baseline blood glucose concentration. A supplemental intravenous insulin infusion was not employed in this study.

Measurements

Flow-volume spirometry (FEV₁ and FVC) was conducted at screening and prior to discharge. In addition, FEV₁ and FVC were measured via a portable spirometer for glucose clamps involving pulmonary dosing. Recordings were made within 90 min before initial dosing and within 60 min after the end of the glucose clamp procedure.

There were two distinct biochemical measurements in this study, serum exposure level of insulin (PK) and glucose action profiles (GD). Thus, we defined the relative exposure of insulin as bioavailability and the relative glucose activity as biopotency. Total serum immunoreactive insulin (IRI) levels were collected at regular intervals. Total IRI in human serum was analysed using a validated radioimmunoassay method. Following pulmonary and s.c. insulin dosing, maximum serum insulin concentration ($C_{\max}$), the time of maximum serum insulin concentration ($T_{\max}$), and the area-under-the-serum-insulin-time curve (AUC_{INS}) were assessed. AUC_{INS} was calculated using a linear/log trapezoidal method in WinNonLin® (Professional Edition, Version 2.1, Pharsight, Cary, NC, USA). Continuously registered glucose infusion rates (GIR) allowed the estimation of maximal glucose infusion rate ($\text{GIR}_{\max}$), and time to maximal glucose infusion rate ($\text{GIR } T_{\max}$). Specifically, for calculation of $\text{GIR}_{\max}$ and $\text{GIR } T_{\max}$, a polynomial function of 6th order was fitted to individual GIR profiles. The area-under-the-curve for GIR profiles for 10 h after insulin dosing (GIR_{tot}) was computed using the linear trapezoidal method.

Statistical analysis

A power model was used to estimate dose-equivalence between pulmonary and s.c. insulin, relative bioavailability based on AUC_{INS} , relative biopotency based on GIR_{tot} , and the corresponding variances. A linear MIXED effects model was derived from the log-transformed responses, which was equivalent to the power model on the logarithm scale. The MIXED procedure in the SAS© System (v. 6.12) for Windows® was used to obtain the model estimates.

Procedure IML in SAS® System (v. 6.12) for Windows® was used to estimate the relative bioavailability, relative biopotency, and dose-equivalence. Fieller's theorem [12] was used to estimate the 95% confidence interval for the relative bioavailability, relative biopotency, and dose equivalence



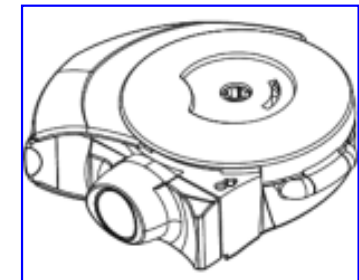
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Table 2 Relative bioavailability and relative biopotency of four doses of inhaled insulin vs. three di...



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Table 3 (a) Intra- and (b) inter-subject CV of AUC_{INS} and GIR_{tot}



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Figure 1 Spiros® blisterdisk dry powder inhaler delivery device.

between inhaled and s.c. insulin. Intra- and inter-subject coefficient of variation (%) estimates and corresponding 95% confidence intervals were calculated using the variance estimates from the power model (MIXED procedure) in the SAS© System.

Time to maximal glucose infusion rate (GIR T_{max}) and time to maximum insulin concentration (T_{max}) statistical analyses were carried out with SAS© Procedure NPAR1WAY. Treatment medians for the two routes of insulin administration and the *P*-value for the hypothesis of 'no treatment difference' were computed using the Wilcoxon signed-rank test.

Results

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Volunteer disposition

Thirteen healthy volunteers were randomised into the study (eight female and five male), of whom 11 completed the protocol. One volunteer was discontinued due to missing dose and treatment records. A second volunteer discontinued for personal reasons and received only the PK portion (inhalation 3, 4 and 5) without the corresponding s.c. treatment, thus dose-response and dose-equivalence analyses were not possible for these volunteers. However, data from these two individuals were included in the safety analyses. Data from the 11 volunteers who completed the protocol were included in the PK, PD, bioavailability, biopotency, and statistical analyses. The mean ($\pm$ sd) age of the volunteers was 30 ± 7 years with a minimum of 22 years and a maximum of 42 years. Body mass index (BMI) was 23.5 ± 2.7 kg/m².

Safety

There were no pregnancies, deaths, or other serious adverse events. The most commonly reported adverse event was headaches (in three subjects for a total of eight episodes). It was not clear whether these headaches were directly related to dose or the glucose clamp procedure. FVC and FEV₁ at screening (5.82 L and 4.91 L) were not statistically significantly different from the final study visit (Δ FVC = -0.24 L, *P* = 0.12; Δ FEV₁ = -0.21 L, *P* = 0.20). There were no significant changes in mean vital signs between the final study visit and the screening visit.

Pharmacokinetics and glucodynamics

Pharmacokinetic and glucodynamic summary parameters are shown in Table 1. On average, serum insulin with inhaled insulin peaked 60 min earlier (T_{max}) compared with s.c. insulin (*P* < 0.0001) (Fig. 2). Following inhalation, GIR_{max} peaked 70 min earlier than with s.c. insulin (*P* < 0.0001) (Fig. 3). The mean T_{max} across all doses for pulmonary insulin was 60 min and 120 min for s.c. insulin, respectively. T_{max} was consistent across the dose range studied. A linear dose-response relationship was observed for both pulmonary and s.c. insulin (Fig. 4). The slope of the log transformed dose-response curve did not appear to be different from one. Dosing was well tolerated by all volunteers.

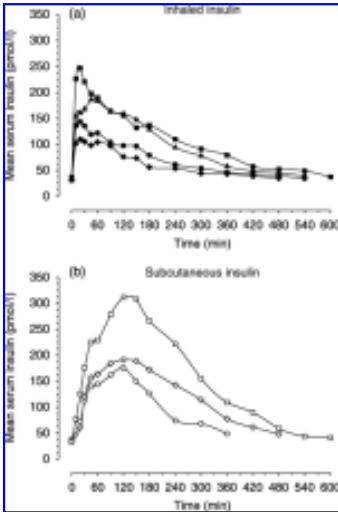
Relative bioavailability and relative biopotency for the four different doses of pulmonary insulin vs. three doses of s.c. insulin are given in Table 2. The mean relative bioavailability based on AUC_{INS} ranged from 11.5 to 12.2% and the relative biopotency based on GIR_{tot} dose ranged from 10 to 16.5%. Intra- and inter-subject variability estimates of pulmonary insulin responses were comparable with that of s.c. insulin (Table 3a and b).

Discussion

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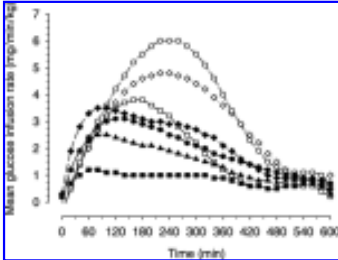
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Pulmonary insulin can be formulated as either a liquid or dry powder aerosol.



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Figure 2 (a) Serum insulin for inhaled regular human insulin, 60 U inh (◆), 90 U inh (●), 120 U inh (▲) and ...



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Figure 3 Glucose infusion rate for inhaled and s.c.-injected regular human insulin. Curves are 6th ord...

Dry powder insulin formulations have better chemical stability, can deliver more insulin per inhalation, and are less likely to experience microbial growth [3]. This is the first study investigating dose-response, dose-equivalency, safety and tolerability of a unique micronized crystalline inhaled insulin formulation delivered by a hand-held dry powder inhaler (DPI). Inhaled insulin was more rapidly absorbed, resulting in peak serum insulin levels 60 min earlier (T_{max}) than with s.c. insulin. After inhalation, the time to maximum glucose infusion rate (GIR T_{max}) was 70 min earlier than with s.c. insulin. Dose-response and time-action profiles of this unique micronized crystalline inhaled insulin formulation were similar to those reported in other studies in healthy volunteers [6,7].

Inhaled micronized crystalline insulin with its rapid onset of action mimicked the pharmacokinetic and pharmacodynamic properties of s.c.-injected rapid-acting insulin analogues. However, in contrast to these analogues, the metabolic activity of inhaled insulin decreased slowly, showing some residual metabolic effect extending beyond 6 h. In this regard, inhaled insulin resembled s.c. regular human insulin. These combined features, i.e. rapid achievement of peak action, followed by a slow decline of metabolic activity, may provide an excellent means for substituting prandial insulin needs.

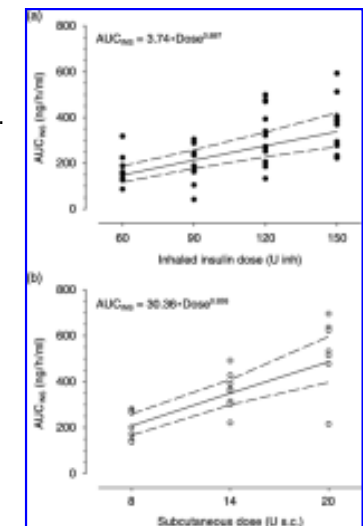
The overall biopotency of human insulin delivered by inhalation relative to s.c. regular human insulin in this study was approximately 11%, and it was consistent across the pulmonary insulin dose range studied. In previous studies, the relative bioavailability and biopotency of pulmonary insulin compared with s.c. regular human insulin ranged from 5 to 26%, depending upon the formulation, size of the molecule and type of delivery device [3,6,13,14]. Thus, our result is comparable with the relative biopotency of inhaled insulin reported by other investigators [3,6,13,14].

The relative biopotency of 11% required approximately a 10-fold dose be inhaled to achieve a serum insulin or glucose response equivalent to s.c. insulin. The HIIP used in this study exhibited a distinct time-action profile as compared with s.c. insulins, including either fast-acting insulin analogues (which have similar fast onset but shorter duration of action), or regular human insulin (which has slower onset but similar duration of action). Definitive analysis to identify the dosage requirement for meal-time usage of HIIP based on the observed bioavailability and biopotency estimates has not been performed at this time.

Intra-subject variability estimates are important measures of dose reproducibility for inhaled insulin. It is of high clinical relevance to identify if repeated inhalations of the same dose produce predictable and reproducible responses in the same patient. The inter-subject variability of pulmonary insulin measured in this study was comparable with that of s.c.-injected regular human insulin.

This result concurs with Heinemann *et al.* (2000) who addressed intrasubject variability of inhaled insulin in a controlled study of 13 healthy male volunteers. They found the variability in the induced metabolic effect was comparable with that of regular human insulin following s.c. administration [13]. However, a limitation of our study was that intra-subject variability was only estimated with a general assumption of no-dose effect on variability. None of the subjects in this study received the same dose more than once. A more elaborate PK/PD model for serum insulin and glucose clamp data is needed to effectively study the impact of administration routes on the variability of the dose-response relationships.

In summary, this study demonstrates that inhalation of a micronized crystalline human insulin aerosol using a dry powder inhaler was well tolerated and poses a promising alternative route of insulin delivery for the treatment of diabetes. However, a better understanding of the impact of particle aerodynamics and absorption kinetics on the reproducibility of glucodynamic response is essential for furthering this alternative. As the technology continues to develop, long-term safety, cost and patient acceptance will determine whether inhaled insulin becomes a practical treatment option for insulin therapy.



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Figure 4 Linear dose-response curves for (a) inhaled (•) and (b) s.c.-injected (•) regular human insulin...

To cite this article

Rave, K., Nosek, L., Heinemann, L., Gonzales, C., Ernest, C. S., Chien, J. & Muchmore, D. (2004) Inhaled micronized crystalline human insulin using a dry powder inhaler: dose-response and time-action profiles¹. *Diabetic Medicine* **21** (7), 763-768. doi: 10.1111/j.1464-5491.2004.01240.x

Acknowledgements

The authors would like to acknowledge Elaine Phillips (system development team leader) and Malcolm Hill (clinical leader from Dura Pharmaceuticals Aerosol Research Laboratories) for their collaborative efforts on this project. Appreciation is expressed to Ms Kathryn Gilmore for preparation of the manuscript and to Ms Margaret Campbell and Mr Anthony Reitz for editorial assistance. This study was sponsored by Eli Lilly and Company.

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Abstract

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Table 1 Pharmacokinetic and glucodynamic summary measures for inhaled and s.c. regular human insulin

	C_{max} pmol/l	T_{max}* (min)	GIR_{max} (mg/min/kg)	GIR T_{max} (min)	GIR_{tot} (g)
8 U s.c.	184 ± 43.5	120 (90–150)	4.1 ± 1.3	227 ± 153	73 ± 23
14 U s.c.	205 ± 67.7	105 (30–300)	5.1 ± 2.7	241 ± 73	120 ± 56
20 U s.c.	353 ± 128	120 (20–150)	6.1 ± 2.5	241 ± 29	131 ± 42
60 U inh	140 ± 66.8	30 (10–90)	2.0 ± 0.8	187 ± 136	35 ± 17
90 U inh	183 ± 78.0	20 (10–150)	3.3 ± 1.8	129 ± 86	63 ± 44
120 U inh	223 ± 95.0	45 (10–120)	3.4 ± 1.7	161 ± 129	79 ± 44
150 U inh	273 ± 126	20 (10–240)	4.2 ± 1.9	162 ± 118	89 ± 33
Mean ± sd. inh, inhaled insulin; C _{max} , maximum serum insulin concentration; *T _{max} , time of maximum serum insulin concentration (median and range); GIR _{max} , maximum glucose infusion rate; GIR T _{max} , time of maximum glucose infusion rate; GIR _{tot} , total amount of glucose infused.					

Table 2 Relative bioavailability and relative biopotency of four doses of inhaled insulin vs. three different doses of s.c. insulin

Inhaled dose	Bioavailability AUC _{INS} (95% CI)	Biopotency GIR _{tot} (95% CI)
60 U	12.2% (9.6%, 15.3%)	16.5% (13.6%, 21.7%)
90 U	11.9% (10.1%, 14.8%)	13.3% (11.2%, 17.9%)
120 U	11.7% (9.6%, 15.9%)	11.3% (9.3%, 16.3%)
150 U	11.5% (8.9%, 15.9%)	10.0% (7.9%, 15.4%)
AUC _{INS} , serum insulin area-under-the-curve; GIR _{tot} , total amount of glucose infused.		
Mean (95% confidence interval (CI)).		

Table 3 (a) Intra- and (b) inter-subject CV of AUC_{INS} and GIR_{tot}

(a)

Route of insulin administration	Parameter	CV%	95% CI
Pulmonary	AUC _{INS}	33.1	(26.5%, 44.3%)
	GIR _{tot}	58.4	(45.7%, 81.9%)
Subcutaneous	AUC _{INS}	25.4	(17.6%, 46.2%)
	GIR _{tot}	25.9	(17.9%, 46.8%)

(b)

Route of administration	Parameter	CV%	95% CI
Pulmonary	AUC _{INS}	28.1	(17.8%, 68.5%)
	GIR _{tot}	38.4	(22.6%, 140.8%)
Subcutaneous	AUC _{INS}	18.5	(9.6%, 151.4%)
	GIR _{tot}	41.9	(22.6%, 99.9%)
AUC _{INS} , serum insulin area-under-the-curve; GIR _{tot} , total amount of glucose infused; CV, coefficient of variance; CI, confidence interval.			

Figure 1 Spiros® blisterdisk dry powder inhaler delivery device.

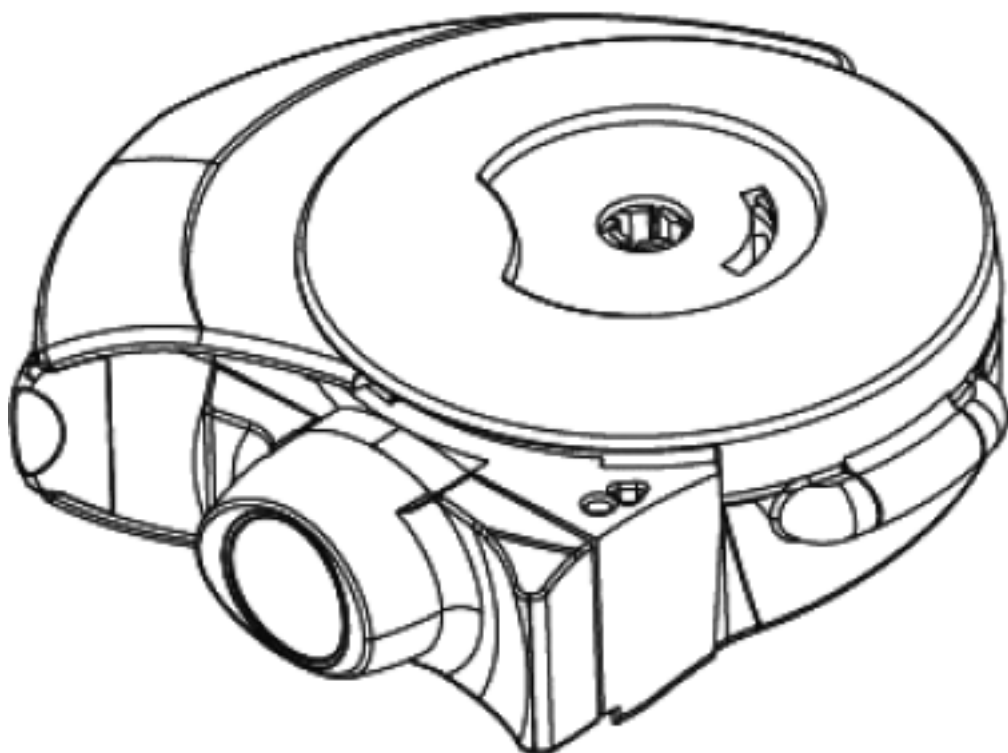


Figure 2 (a) Serum insulin for inhaled regular human insulin, 60 U inh (◆), 90 U inh (●), 120 U inh (▲) and 150 U inh (■). (b) Serum insulin for s.c.-injected regular human insulin, 8 U s.c. (○), 14 U s.c. (◇) and 20 U s.c. (◻).

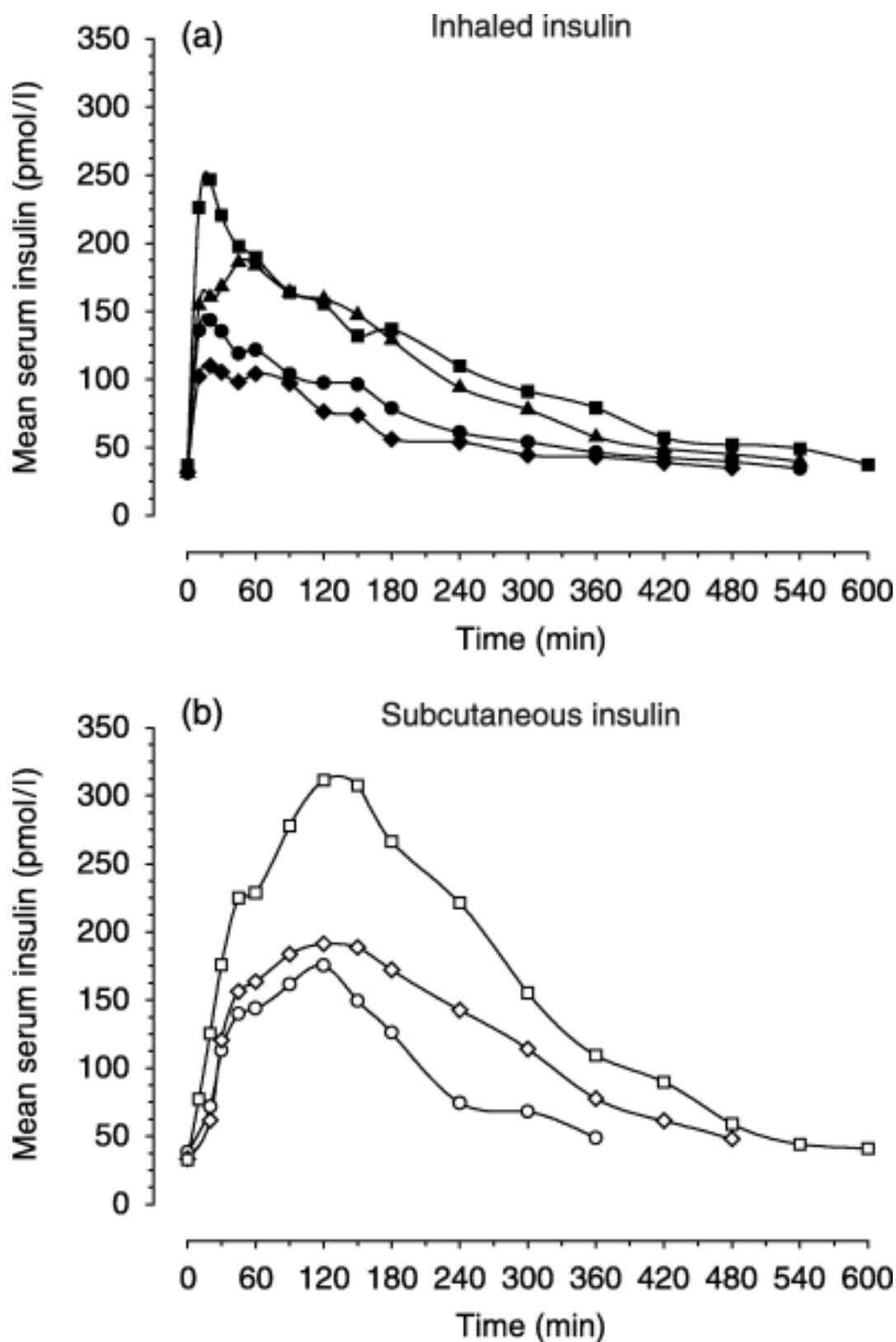


Figure 3 Glucose infusion rate for inhaled and s.c.-injected regular human insulin. Curves are 6th order polynomial fittings to the mean glucose infusion rates across all study subjects. 8 U s.c. (○), 14 U s.c. (◇), 20 U s.c. (●), 60 U inh (■), 90 U inh (▲), 120 U inh (•), 150 u inh (◆).

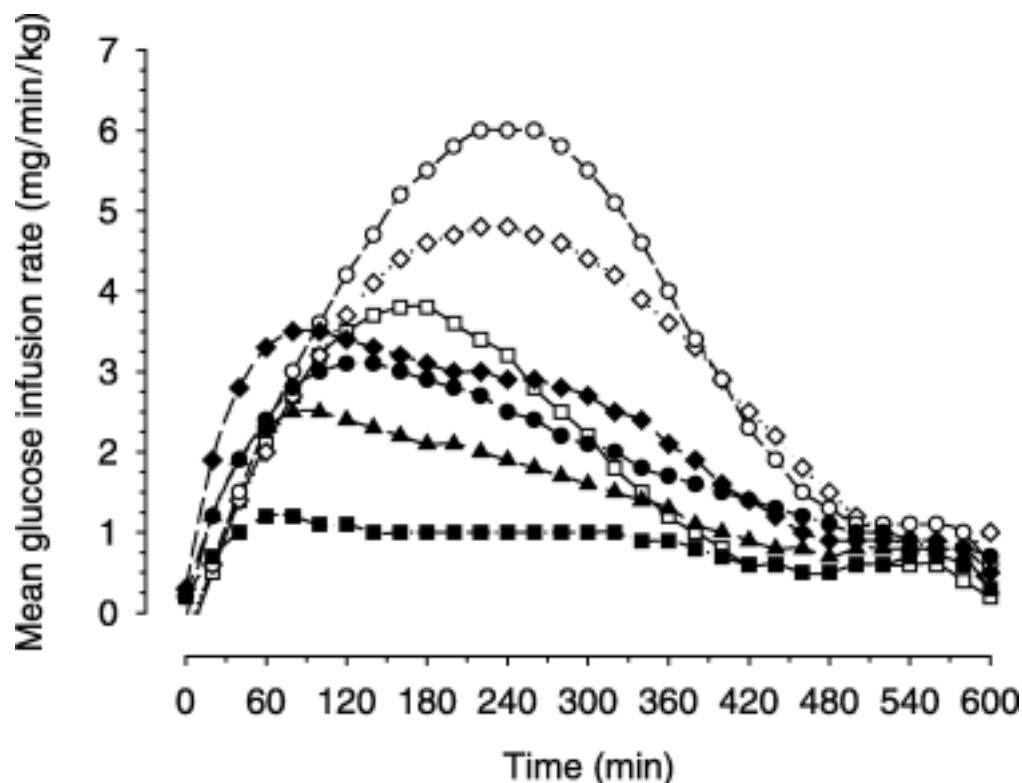


Figure 4 Linear dose-response curves for (a) inhaled (•) and (b) s.c.-injected (○) regular human insulin based on AUC_{INS} (area-under-the-serum-insulin-curve). Linear regression equation is shown along with 95% confidence interval.

