Diabetologia (2001) 44: 305–308

Diabetologia

Short communication

Dose-response relation of liquid aerosol inhaled insulin in Type I diabetic patients

G. A. Brunner[1], B. Balent[1], M. Ellmerer[1], L. Schaupp[1], A. Siebenhofer[1], J. H. Jendle[2], J. Okikawa[3], T. R. Pieber[1]

[1] Department of Internal Medicine, Karl-Franzens University, Graz, Austria
[2] Novo Nordisk A/S, Copenhagen, Denmark
[3] Aradigm Corp., Hayward, California, USA

Abstract

Aims/hypothesis. The AERx insulin Diabetes Management System (AERx iDMS) is a liquid aerosol device that enables insulin to be administered to the peripheral parts of the lung. This study aimed to compare the pharmacokinetic and pharmacodynamic properties of insulin which is inhaled using AERx iDMS with insulin which is subcutaneously administered.
Methods. In total, 18 C-peptide negative patients with Type I (insulin-dependent) diabetes mellitus participated in this randomised, open-label, 5-period crossover trial. Human regular insulin was administered subcutaneously (0.12 U/kg body weight) or inhaled by means of the AERx iDMS (dosages 0.3, 0.6, 1.2, and 1.8 U/kg body weight). Thereafter plasma glucose was kept constant at 7.2 mmol/l for a 10-h period (glucose clamp technique).
Results. Inhaled insulin provided a dose-response relation that was close to linear for both pharmacokinetic (AUC-Ins$_{(0–10\,h)}$; Cmax-Ins) and pharmacodynamic (AUC-GIR$_{(0–10\,h)}$; GIRmax) parameters. Time to maximum insulin concentration (Tmax-Ins) and time to maximum glucose infusion rate (TGIRmax) were shorter with inhaled insulin than with subcutaneous administration. The pharmacodynamic system efficiency of inhaled insulin (AUC-GIR$_{(0–6\,h)}$) was 12.7% (95% C.I.: 10.2–15.6).
Conclusion/interpretation. The inhalation of soluble human insulin using the AERx iDMS is feasible and provides a clear dose response. Further long-term studies are required to investigate safety aspects, HbA_{1c} values, incidence of hypoglycaemic events and the quality of life. [Diabetologia (2001) 44: 305–308]

Keywords Type I diabetes, inhaled insulin, pulmonary insulin, pharmacokinetics, pharmacodynamics, insulin therapy.

Received: 18 July 2000 and in revised form: 25 October 2000

Corresponding author: G.A. Brunner, MD, Department of Internal Medicine, Karl-Franzens University, Auenbruggerplatz 15, A-8036 Graz, Austria
Abbreviations: AERx iDMS, AERx insulin Diabetes Management System; AUC, area under the curve; Cmax-Ins, maximum concentration of serum insulin; Tmax-Ins, time to Cmax; GIR, glucose infusion rate; GIRmax, maximum glucose infusion rate; TGIRmax, time to maximum glucose infusion rate; s.c., subcutaneous; CSII, continuous subcutaneous insulin infusion; PK/PD, pharmacokinetic/pharmacodynamic; C.I., confidence interval.

In order to optimise insulin treatment, insulin analogues for subcutaeous injection have been designed recently [1]. Substantial efforts have also been directed towards finding alternative routes for insulin administration [2]. The AERx insulin Diabetes Management System (AERx iDMS) is a device enabling liquid aerosols of insulin to be administered into the peripheral parts of the lung by inhalation [3]. It emits a fine particle aerosol (mass median aerodynamic diameter 2–3 μm) from single-use dosage forms by extruding the pre-packaged solution through hundreds of precisely laser-drilled holes in a single-use nozzle. This study aimed to investigate the pharmacokinetic and pharmacodynamic properties of different doses

of inhaled insulin and to compare them with subcutaneous insulin. For this purpose a randomised, open-labelled, 5-period cross-over trial was carried out.

Subjects and methods

Subjects. A total of 18 Type I (insulin-dependent) diabetic patients (11 men) participated in the trial. All patients were non-smokers, had fasting C-peptide concentrations less than 0.5 nmol/l and were on an intensive insulin therapy programme. None of the patients had overt diabetic nephropathy, rapidly progressing diabetes-related complications or any evidence of lung disease as assessed by chest X-ray and lung function tests. The main characteristics (mean ± SD) of the patients were: age 35.4 ± 5.9 years; BMI 24.0 ± 1.9 kg/m^2, body weight 72.6 ± 8.8 kg; HbA_{1c} 8.1 ± 0.9 %. The study was approved by the ethics committee of the Karl-Franzens University and all patients gave their written and informed consent before commencing the trial. On study days, patients were admitted at 0730 h after an overnight fast and remained fasting and in supine position during the entire study day. Patients on subcutaneous treatment omitted their morning insulin and patients on continuous subcutaneous insulin treatment (CSII) stopped their insulin infusion upon admission. At 0800 h, a hand vein was cannulated retrograde and kept in a thermoregulated box (55 °C) to sample arterialized blood [4]. On the contralateral arm, an antecubital vein was cannulated to infuse insulin or glucose. From 0800 h until 1300 h stable euglycaemia (≈ 7.2 mmol/l; range 5.0–9.4) was achieved by a variable infusion of insulin [4]. This intravenous infusion of insulin was tapered according to a standardised protocol during the last 10 min before the dose of inhaled insulin was administered. Immediately after dosing of inhaled insulin (1300 h) intravenous insulin was stopped to exclude any influence on the post-dose pharmacokinetic/pharmacodynamic (PK/PD) results. For the subcutaneous administration regimen (injection at 1300 h) the intravenous infusion of insulin was tapered from 1300 h until 1310 h and then stopped. Patients were chosen at random for distinct treatment sequences selected from 4 orthogonal latin squares (randomisation remote from the study site).

The subcutaneous dose (0.12 U/kg body weight; Actrapid HM Penfill 100 U/ml; Novo Nordisk; A/S) was injected into a lifted skin fold of the abdominal wall. The inhalation of intrapulmonary insulin (0.3, 0.6, 1.2, and 1.8 U/kg body weight; human soluble insulin in dosage forms of 500, 1000 and 1500 U/ml) was given as follows: insulin aerosol for inhalation was generated by the AERx iDMS only when the inspiratory flow rate was within 50 to 70 l a min after a small volume of initial inhalation. After the inhalation of the trial drug, patients held their breath for 10 s and then exhaled slowly.

After the trial drug dose was administered, plasma glucose was kept constant at 7.2 mmol/l for a 10-h period by variable infusion of glucose 20 % (glucose clamp technique). Between study days (washout interval 4–10 days) the patients continued their usual intensive insulin therapy.

Analytical methods. Plasma glucose was measured in duplicate using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, Calif., USA) at 5 to 15 min intervals. Plasma insulin was measured by a commercially available RIA (Pharmacia, Uppsala, Sweden) at 5 to 60 min intervals. Fasting C-peptide was measured during the screening visit (DAKO Diagnostics, Cambridgeshire, UK).

Calculations. The areas under the curve were calculated by the trapezoidal rule. The maximum concentration of serum insulin (Cmax-Ins) maximum glucose infusion rate (GIRmax) time to maximum concentration of serum insulin (Tmax-Ins) and time to maximum glucose infusion rate (TGIRmax) were derived from the profiles of serum insulin and glucose infusion rate and from the time interval from 0 to 10 h after dosing. The term system efficiency was used to define the relative bioavailability based on the loaded dose of inhaled insulin, as opposed to a physiological relative bioavailability based on the dose entering the lung. The former was calculated as the ratio between the AERx dose and subcutaneous dose taking into account the AERx dose that was estimated to give the same results for $AUC\text{-}Ins_{(0–6\,h)}$ and $AUC\text{-}GIR_{(0–6\,h)}$.

Statistical analysis. With regard to AUC-Ins, Cmax-Ins, AUC-GIR and GIRmax, we used polynomial regression models to establish a dose-response relation between the different doses of inhaled insulin. These analyses were carried out on a log scale (log response versus log dose). A comparison of subcutaneous and inhaled insulin was made under the assumption that the response curves had similar shapes.

Results

Mean serum insulin profiles and mean glucose infusion rates are given in Figure 1A and B. The area under the insulin curve [$AUC\text{-}Ins_{(0–10\,h)}$] and maximum serum insulin concentration [Cmax-Ins] showed a clear dose response after pulmonary insulin administration (Table 1, Fig. 1C). This relation was linear on a log-log scale and close to linear on the ordinal scale. Similarly, the pharmacodynamic results showed close to linear relations of maximum glucose infusion rate [GIRmax] and area under the GIR profile [$AUC\text{-}GIR_{(0–10\,h)}$] (Table 1, Fig. 1D). Time to maximum insulin concentration (Tmax-Ins) and time to maximum glucose infusion rate ($TGIR_{max}$) were shorter with inhaled insulin than with subcutaneous treatment (Table 1). The intra-subject variability (calculation based on dosages of 0.6 and 1.2 U/kg) was estimated to be 25.8 % for $AUC\text{-}Ins_{(0–10\,h)}$ and 34.2 % for $AUC\text{-}GIR_{(0–10\,h)}$. The system efficiency of insulin administration with the AERx iDMS was estimated to 12.9 % (95 % CI: 10.7–15.6) based upon $AUC\text{-}Ins_{(0–6\,h)}$ and to 12.7 % (95 % CI: 10.2–15.6) based upon $AUC\text{-}GIR_{(0–6\,h)}$. No safety concerns with regard to pulmonary function were raised by this study.

Discussion

To date, several delivery systems for the administration of inhaled insulin, using different formulations, doses and particle sizes of the aerosol, have been investigated in clinical trials [5]. The dose-response relation under standardised conditions has not, however, been studied thus far. Our study shows that fine-particle aerosol-inhaled insulin provides a dose-response relation that is close to linear in Type I diabet-

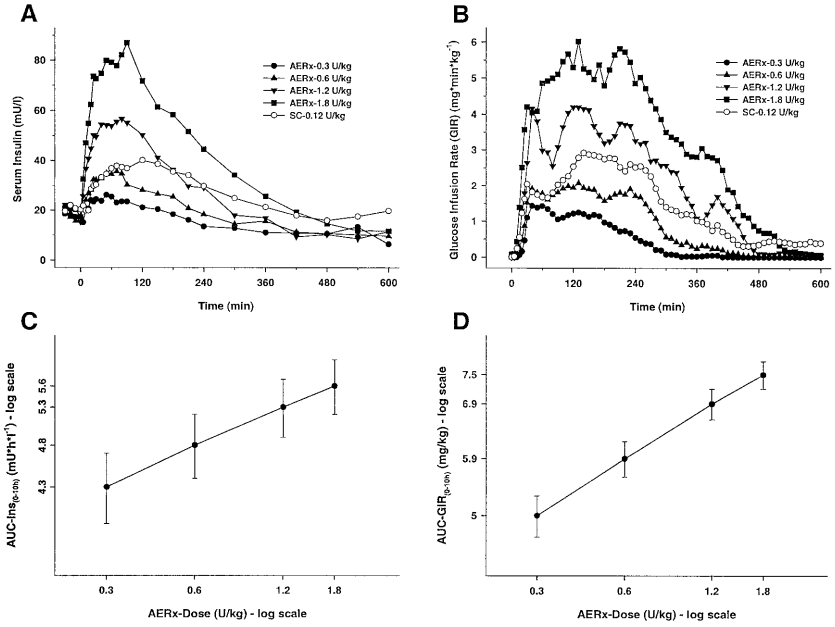

Fig. 1. Mean serum insulin profiles (**A**) and mean glucose infusion rates (**B**) over 10 h after administration of the different treatments at 0 min. Dose-response relation of the area under the insulin curve [AUC-Ins$_{(0-10\,h)}$] (**C**) and the area under the GIR profile [AUC-GIR $_{(0-10\,h)}$] (**D**) over 10 h after administration of 4 different doses of human regular insulin by means of the AERx iDMS. Estimated dose-response relation with 95 % confidence interval (C. I.)

ic patients. Moreover, in accordance with previously published reports [5, 6], our data indicate that inhaled insulin offers a more rapid onset of action (Tmax-Ins and TGIRmax) than subcutaneous administered insulin. Recently, a study in healthy subjects [6] compared single doses of microcrystalline dry powder inhaled insulin and subcutaneous insulin during a glucose clamp. In agreement with our results a more rapid increase to maximum serum insulin concentrations and subsequently a faster onset of action of inhaled insulin compared with subcutaneous administration was found. Though this study [6] was not designed to investigate bioavailability, the relative effectiveness of inhaled insulin with respect to subcutaneous insulin was calculated to be about 8 %. In our study, the system efficiency of pulmonary insulin averaged 13 % during the time period from 0 to 6 h, based on the loaded dose. This finding of reduced bioavailability is probably related to [5] the loss of insulin from the device itself, as well as to a loss of insulin when particles are deposited in mouth and throat or are exhaled again, and, finally, to local intrapulmonary degradation of insulin even after the optimal inhalation of the aerosol. Reduced bioavailability is found in all systems used for administration of inhaled insulin and seems to be insurmountable as yet [5].

Another device for the delivery of nebulized insulin to the lung has recently been investigated in patients with Type II (non-insulin-dependent) diabetes mellitus [7]. In this non-randomised, placebo-controlled, two-period crossover study, postprandial blood glucose concentrations were significantly lower after pulmonary insulin administration when compared with placebo. Moreover, a dry powder insulin

Table 1. Pharmacokinetics and pharmacodynamics of the different treatments

	Treatment and insulin dose				
	AERx-0.3 U/kg	AERx-0.6 U/kg	AERx-1.2 U/kg	AERx-1.8 U/kg	SC-0.12 U/kg
AUC-Ins$_{(0-10\,h)}$ (mU · h · l^{-1})	79 (10–477)	122 (30–514)	200 (49–671)	315 (98–1125)	184 (90–739)
Cmax-Ins (mU/l)	23.4 (9.3–83.7)	32.9 (13.7–95.8)	53.8 (14.2–142.5)	77.4 (24.8–216.7)	35.1 (16.5–122.3)
Tmax-Ins (min)$^{\beta}$	49 (0–120)	48 (25–80)	62 (25–120)	65 (25–120)	119 (10–300)
AUC-GIR$_{(0-10\,h)}$ (mg/kg)	165 (13–499)	452 (240–943)	1029 (192–2209)	1695 (772–3442)	765 (401–1321)
GIRmax (mg · min · kg^{-1})	1.6 (0.5–3.0)	2.5 (1.4–4.3)	4.7 (2.0–9.0)	6.5 (3.5–14.0)	3.2 (2.4–6.0)
TGIRmax (min)$^{\beta}$	94 (30–210)	136 (40–250)	157 (40–270)	218 (90–350)	189 (40–390)

AUC-Ins; area under the serum insulin curve; Cmax-Ins, maximum concentration of serum insulin; Tmax-Ins, time to Cmax-Ins; AUC-GIR, area under the curve of the glucose infusion rate; GIRmax, maximum GIR; TGIRmax, time to GIRmax

Data are geometric mean except for [$^{\beta}$ calculated mean] and range

formulation administered by means of an aerosol delivery device was investigated over a 3-month period in Type I and Type II diabetic patients [8, 9]. In these studies, metabolic control after 3 months did not change. No increase in hypoglycaemic events was observed, but the quality of life, as assessed by a satisfaction questionnaire, was improved. Even if 3-month data would be available now for pulmonary insulin administration [8, 9], no definite conclusions can, however, be drawn about the long-term safety aspects with regard to adverse toxic or immunological reactions in the pulmonary tissue. Although studies so far have not reported adverse lung or immune reactions after the inhalation of insulin [5, 10], further knowledge regarding the long-term effects of inhaled insulin on lung tissue and longer lasting clinical studies including results of pulmonary function tests, are strongly recommended.

In conclusion, this study shows feasibility and a clear dose response of inhaled aerosol insulin administered by means of the AERx iDMS. Moreover, the more rapid onset of action of pulmonary insulin, which seems to be similar to that of short-acting insulin analogues [1], might be advantageous when inhaling short-acting insulin to cover prandial insulin requirements in intensive insulin therapy. To assess clinical relevance of insulin administered using the AERx iDMS, further long-term studies investigating safety aspects, HbA_{1c} values, incidence of hypoglycaemic events and quality of life are required.

Acknowledgements. Support for this study was provided by Novo Nordisk A/S, Denmark.

References

1. Bolli GB, Di Marchi RD, Park GD, Pramming S, Koivisto VA (1999) Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia 42: 1151–1167
2. Saudek CD (1997) Novel forms of insulin delivery. Endocrinol Metab Clin North Am 26: 599–610
3. Jendle JH, Karlberg BE (1996) Intrapulmonary insulin administration to healthy volunteers. J Intern Med 240: 93–98
4. Brunner GA, Hirschberger S, Sendlhofer G et al. (2000) Post-prandial administration of the insulin analogue insulin aspart in diabetes mellitus. Diabet Med 17: 371–375
5. Patton JS, Bukar J, Nagarajan S (1999) Inhaled insulin. Adv Drug Deliv Rev 35: 235–247
6. Heinemann L, Traut T, Heise T (1997) Time-action profile of inhaled insulin. Diabet Med 14: 63–72
7. Laube BL, Benedict GW, Dobs AS (1998) The lung as an alternative route of delivery for insulin in controlling postprandial glucose levels in patients with diabetes. Chest 114: 1734–1739
8. Phase II Study Group (1998) Treatment of type I diabetes mellitus with inhaled insulin: a 3-month multicenter trial. Diabetes 47 [Suppl 1] A61 (Abstract 236)
9. Phase II Study Group (1998) Treatment of type II diabetes mellitus with inhaled insulin: a 3-month multicenter trial. Diabetes 47 [Suppl 1] A61 (Abstract 237)
10. Wolff RK (1998) Safety of inhaled proteins for therapeutic use. J Aerosol Med 11: 197–219