

Treatment with intravenous insulin followed by continuous subcutaneous insulin infusion improves glycaemic control in severely resistant Type 2 diabetic patients

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Abstract

Aims Despite high-dose s.c. insulin therapy, some Type 2 diabetes mellitus (DM) patients remain in poor metabolic control. We investigated whether a period of euglycaemia using i.v. insulin, followed by continuous subcutaneous insulin infusion (CSII), would ameliorate the deleterious effects of hyperglycaemia on insulin sensitivity and result in sustained, improved metabolic control.

Methods In a prospective observational study, eight Type 2 DM patients with severe insulin resistance (insulin dose 1.92 ± 0.66 U/kg per day (mean \pm SD)), in poor metabolic control (HbA_{1c} $12.0 \pm 1.7\%$), were treated with i.v. insulin for 31 ± 10 days aimed at euglycaemia, followed by CSII therapy for 12 months, using insulin lispro. Before and after 28 ± 6 days of i.v. insulin treatment, insulin sensitivity was measured by a hyperinsulinaemic euglycaemic clamp.

Results Euglycaemia was reached after 12 ± 6 days of i.v. insulin treatment. Subsequently, the i.v. insulin dose required to maintain euglycaemia decreased from 1.7 ± 0.9 to 1.1 ± 0.6 U/kg per day ($P < 0.005$). Whole body glucose uptake increased from 12.7 ± 5.7 to 22.4 ± 8.8 $\mu\text{mol/kg}$ per min ($P < 0.0005$). HbA_{1c} decreased to $8.9 \pm 1.2\%$ after 28 ± 6 days, to $7.1 \pm 0.6\%$ after 6 months and to $8.3 \pm 1.4\%$ after 12 months ($P < 0.001$ vs. pretreatment, for all). Lipid profile improved and plasminogen activator inhibitor type 1 levels decreased significantly. Mean body weight did not change.

Conclusions In Type 2 diabetic patients, who are poorly controlled despite high-dose s.c. insulin treatment, a period of 2 weeks of euglycaemia achieved by i.v. insulin reverses hyperglycaemia-induced insulin resistance and substantially improves metabolic control. Subsequent CSII treatment, using insulin analogues, appears to maintain improved metabolic control for at least 1 year. This approach is promising but needs further evaluation.

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Keywords Type 2 diabetes, insulin resistance, treatment, CSII, insulin

Introduction

Although Type 2 diabetes mellitus (DM) can be treated with diet, exercise and oral hypoglycaemic agents, transfer to insulin is

often necessary [1]. This usually results in adequate glycaemic control but some patients remain inadequately controlled despite intensive treatment with large insulin doses, apparently not responding to further increase in insulin dose. Under these circumstances, persisting chronic hyperglycaemia may have a deleterious impact on insulin action and secretion (conceptualized as glucose toxicity), thereby perpetuating and aggravating insulin resistance and poor metabolic control [2].

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We hypothesized that a protocol consisting of i.v. insulin directed at euglycaemia, followed by continuous subcutaneous insulin infusion (CSII) using insulin analogues, might ameliorate the hyperglycaemia-induced insulin resistance and achieve sustained, improved metabolic control.

Patients and methods

Patients were recruited over 2 years. They had severe insulin resistance, defined as an insulin dose > 1.5 U/kg per day, and sustained poor glycaemic control (HbA_{1c} $12.0 \pm 0.6\%$). They were investigated in a prospective, observational study. All patients had been initially treated with oral hypoglycaemic drugs, thereafter with a conventional split-mixed insulin regimen and finally with a four-dose insulin regimen (s.c. insulin dose 1.92 ± 0.66 U/kg per day). Three patients were also treated with metformin. HbA_{1c} , body mass index (BMI) and insulin treatment were stable for > 3 months before inclusion.

Protocol

In-patient period

Patients were hospitalized and treated with i.v. insulin (Actrapid®) aiming for euglycaemia. In addition, patients received diabetes education, diet instructions (1500 kcal/24 h) and were encouraged to exercise on a bicycle two to four times a day. Metformin was added in increasing dosages. All patients recorded their capillary blood glucose (CBG) four times daily; fasting, pre-lunch, pre-supper and at bedtime. Nurses measured CBG at 3 a.m.

I.V. insulin was given continuously (basal schedule) and a bolus of i.v. insulin given before each meal (bolus schedule). The insulin dose was individually titrated by the same clinician (M.-J.P.). Glycaemic treatment goal was: CBG 4.0–6.5 mmol/l. Insulin dose was increased until all CBG measurements over the whole 24-h period were on target. Subsequently, insulin dose required to maintain euglycaemia and to avoid hypoglycaemic values gradually decreased. I.V. insulin was continued until no further decrease in the daily insulin dose was observed.

In vivo insulin sensitivity was measured using a hyperinsulinaemic euglycaemic clamp [3], before (day 2) and after treatment with i.v. insulin for 28 ± 6 days. During the clamp, insulin (Actrapid®; Novo-Nordisk, Denmark), diluted in 100 ml 0.9% NaCl with addition of 4 ml albumin to a concentration of 2 U/ml, was infused in a dose of 120 mU/m² per min (720 pmol/m² per min) for 4 h.

On the days of the clamp other metabolic parameters were measured under fasting conditions.

After i.v. insulin, patients started on CSII (H-tron®; Disetronic Medical Systems, Burgdorf, Switzerland) using an insulin analogue (Humalog®, insulin lispro; Lilly, USA) in a similar dose and schedule to that during i.v. insulin treatment. Patients were discharged after proper instruction.

Out-patient period

Patients were seen as out-patients every 3 months. Home glucose monitoring (four times daily) was reviewed and insulin dose

adjusted if CBG was repeatedly > 8 mmol/l or < 4 mmol/l. Insulin doses were also adjusted by telephone contact according to CBG measurements with the same protocol.

Laboratory assays

Plasma glucose was measured using the glucose oxidation method (Glucose Analyser II; Beckman Instruments Inc., Fullerton, USA) and insulin was determined using a double-antibody in-house radioimmunoassay. C-peptide was determined using a kit (Diagnostic Products Corp.; cat. no. KPED1 double antibody, CA 900455597). HbA_{1c} was determined with a high-performance liquid chromatography technique (Bio-Rad Labs B.V., Veenendaal, The Netherlands; reference range 4.8–6.2%). Levels of free fatty acids (FFA), triglycerides, cholesterol and HDL-cholesterol were determined as previously described [4]. Antigen levels of urokinase-type plasminogen activator, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor (PAI) type 1 and the tPA–PAI-1 complexes were measured with ELISA [5,6].

Statistical analysis

Statistical analysis of differences was performed by paired Student's *t*-tests (two-sided). All variables were normally distributed. Correlation was assessed with Spearman's rank method. $P < 0.05$ was considered statistically significant. Results are given as the mean \pm SD.

Results

Baseline measurements

Eight non-smoking, Type 2 DM patients (F:M = 6:2, age 53 ± 13 years (range 32–72), duration of diabetes 7 ± 3 years, BMI 38 ± 5.8 kg/m² and waist–hip ratio 0.97 ± 0.08) without other endocrine disorders participated in the study. Four of the eight patients had hypertension, 1/8 had gout, 8/8 had dyslipidaemia. None had retinopathy, 2/8 had ischaemic heart disease, 1/8 atrial fibrillation, 2/8 nephropathy and 1/8 had neuropathy.

In-patient period

Effect of i.v. insulin on glycaemic control and metabolic parameters

Patients were admitted for 34 ± 12 days and treated with i.v. insulin for 30 ± 9 days. Euglycaemia was achieved after a mean of 12 ± 6 days. Subsequently, i.v. insulin dose required to maintain euglycaemia decreased from 1.7 ± 0.9 to 1.1 ± 0.6 U/kg per day ($P < 0.005$) over 12 ± 3 days. After this period, no further decrease in insulin dose was observed. In total, patients remained euglycaemic for 18 ± 4 days.

After 4 weeks of i.v. insulin treatment, HbA_{1c} , lipid profile and PAI-1 returned towards normal (Table 1).

Subsequently patients started on CSII with insulin lispro with the exception of one who used human insulin because of

Table 1 Effect of a 4-week period (28 ± 6 days) of i.v. insulin on metabolic characteristics in patients with poorly controlled Type 2 DM

	Before	After
Fasting plasma glucose (mmol/l)	12.9 ± 3.0	6.6 ± 1.2****
Mean insulin dose (U/day)	176 ± 88	115 ± 70***
Mean insulin dose (U/kg per day)	1.7 ± 0.9	1.1 ± 0.6**
HbA _{1c} (%)	12.0 ± 1.7	8.9 ± 1.2****
Total cholesterol (mmol/l)	5.40 ± 1.09	4.50 ± 1.10*
HDL-cholesterol (mmol/l)	0.77 ± 0.35	0.86 ± 0.33
LDL-cholesterol (mmol/l)	3.41 ± 1.05	2.94 ± 1.08
Triglycerides (mmol/l)	4.34 ± 3.32	1.91 ± 0.69
NEFA (mmol/l)	1.44 ± 0.64	1.11 ± 0.51
C-peptide (mmol/l)	0.73 ± 0.30	0.78 ± 0.20
uPA (ng/ml)	1.21 ± 0.29	1.17 ± 0.23
PAI-1 (ng/ml)	46.8 ± 18.6	38.9 ± 17.9**
tPA (ng/ml)	2.6 ± 1.1	2.4 ± 1.5
tPA-PAI-1 complexes (ng/ml)	10.5 ± 5.0	9.2 ± 5.4

All parameters were measured after an overnight fast.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

plans for future pregnancy. Patients received pump training for 5 ± 4 days before discharge. Basal and bolus pump s.c. insulin dose was similar to i.v.

Effects of i.v. insulin on insulin sensitivity

Plasma glucose levels during steady state of the clamps were 5.8 ± 0.5 mmol/l before and 5.6 ± 0.6 mmol/l after treatment. Plasma insulin concentrations were similar before (266 ± 157 and 1776 ± 1122 pmol/l) and after treatment (219 ± 92 and 1797 ± 539 pmol/l; baseline and steady state levels (240 min), respectively). After a 4-week period of i.v. insulin whole body glucose uptake increased from 12.7 ± 5.7 to 22.4 ± 8.8 µmol/kg per min ($P < 0.0005$).

A trend towards a significant relationship between the improvement in whole body glucose uptake values and the decrease in insulin dose required to maintain euglycaemia was observed ($r = 0.66$, $P < 0.10$). Weight was similar before (106 ± 20 kg) and after treatment (104 ± 20 kg).

Out-patient period, follow-up

Metabolic response, insulin dosage and weight

HbA_{1c} decreased from 12.0 ± 1.7% before the start of the study to 7.1 ± 0.6% after 6 months ($P < 0.0005$), to 7.6 ± 1.0% after 9 months and to 8.3 ± 1.4% after 1 year ($P < 0.001$ vs. before treatment). S.C. insulin dose decreased from 1.92 ± 0.66 U/kg per day before treatment to 1.51 ± 0.99 after 3 months, to 0.96 ± 0.51 after 6 months ($P < 0.01$), to 1.19 ± 0.60 after 9 months ($P < 0.05$) and to 1.24 ± 0.70 U/kg per day after 1 year ($P < 0.05$, vs. before treatment). Mean weight did not change (106 ± 21 kg before vs. 105 ± 17 kg after 6 months, 107 ± 18 kg after 12 months). Five patients received metformin (three continued, two started).

Hypoglycaemic events, adverse events and general well-being

Patients repeatedly reported minor hypoglycaemic events but severe hypoglycaemia did not occur. If glucose levels decreased below 4 mmol/l repeatedly, insulin dose was adjusted.

No retinal deterioration occurred in these patients, as examined by fundoscopy before start of the study and at follow-up. There were no episodes of infusion site infection. After 1 year all patients elected to remain on CSII.

Discussion

This study shows that in a selected group of obese, severely insulin-resistant Type 2 DM patients, in bad metabolic control despite intensive insulin treatment, sustained improvement in metabolic control can be achieved by i.v. insulin followed by CSII. In addition, patients received a moderate calorie-restricted diet (as advised before), performed minor exercise and were treated with metformin, if tolerated.

On average, 12 days were needed to achieve euglycaemia, which was subsequently maintained for 2 weeks. The glucose clamps and the decrease in insulin dose needed to maintain euglycaemia indicated substantially improved insulin sensitivity. Good glycaemic control was also sustained for at least 1 year.

Other treatment modalities had already been tried before without success. Diet and exercise instructions had been given repeatedly. Metformin had also been tried in most ($n = 7$) patients, but withdrawn in four because of side-effects or lack of efficacy. Finally, s.c. insulin treatment, using intensive, multiple daily injections in escalating doses, had failed.

It has been previously shown that a period of strict metabolic control, either by weight loss [7], sulphonylureas [8] or insulin [9,10], can reverse hyperglycaemia-induced insulin resistance [7–11], but most studies were of short duration [12,13] and did not include insulin-treated patients [7–13]. The patients we studied were more severely insulin-resistant. Our results suggest that even in insulin-treated patients hyperglycaemia-induced insulin resistance can be reversed. In such patients, the time needed for metabolic improvement is approximately 3–4 weeks, in accordance with previously reported studies [9,14,15], with insulin dose decreasing by approximately 40%.

The results of this study were obtained by a combined treatment protocol, consisting of admission, i.v. insulin, diet and exercise instructions and metformin. Being observational in design, this study cannot provide information about the contribution of the individual components of the treatment.

We chose to continue insulin treatment with CSII, because in a trial that compared CSII and conventional insulin in Type 2 DM patients, more achieved tight metabolic control with CSII [16]. We cannot be sure with this study design whether CSII alone would have been as effective.

In conclusion, this study demonstrates that in a selected group of patients characterized by severe insulin resistance, obesity and poorly controlled Type 2 DM, improved metabolic control can be achieved by combining i.v. insulin,

followed by CSII. The benefit of this approach suggested by these limited data needs to be established by larger scale controlled studies.

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