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ORIGINAL ARTICLES

Overnight versus 24 Hours of Continuous Subcutaneous Insulin Infusion as Supplement to Oral Antidiabetic Drugs in Type 2 Diabetes

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Abstract

Background:
Basal continuous subcutaneous insulin infusion (CSII) therapy at a fixed rate may effectively improve glycemic control in patients with type 2 diabetes when oral antidiabetic treatment fails. Regimens of *simple* constant subcutaneous delivery of insulin may provide theoretical advantages in type 2 diabetes.

Methods:
Ten subjects with type 2 diabetes who obtained insufficient glycemic control on oral antidiabetic drugs were included. Following an initial control day, two periods of 3 days with CSII of a rapid-acting insulin analogue, 1.5 IU/h (dose obtained from a preceding study), for 8 hours overnight and for 24 hours, respectively, were carried out in random order. Profiles of serum insulin aspart, serum endogenous insulin, and plasma glucose were recorded.

Results:
Compared to the control day, an 8-hour overnight insulin infusion during a 3-day period improved fasting plasma glucose (FPG) (mean differences ± SEM; Δ59.0 ± 10.1 mg/dl; $p < 0.01$) and 2-hour postprandial plasma glucose (PPPG) (Δ57.8 ± 10.6 mg/dl; $p < 0.01$) after breakfast. Compared to an 8-hour overnight infusion, a 24-hour infusion further improved all three PPPG values after breakfast, lunch, and dinner (Δ28.8 ± 8.1 mg/dl, Δ30.6 ± 8.1 mg/dl, and Δ35.1 ± 7.9 mg/dl; $p < 0.01$). During insulin infusion, only one hypoglycemic episode with PG <55.8 mg/dl and mild symptoms was recorded.

Conclusion:
Continuous subcutaneous insulin infusion with a rapid-acting insulin analogue at a *fixed rate* of 1.5 IU/h, either overnight or for 24 hours, improved glycemic control without safety concerns in patients with type 2 diabetes who had secondary failure to oral antidiabetic drugs. The effect on FPG was similar for both treatments, whereas the effect on PPPG was superior when insulin was infused during the entire 24 hours.

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Abbreviations: (ANOVA) analysis of variance, (AUC) area under the curve, (CSII) continuous subcutaneous insulin infusion, (FPG) fasting plasma glucose, (NPH) neutral protamine Hagedorn, (PG) plasma glucose, (PPPG) postprandial plasma glucose

Keywords: CSII, insulin analogue, insulin aspart, insulin pump, intermittent insulin pump, type 2 diabetes

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Introduction

Type 2 diabetes is a chronic disease with a rapid growth in prevalence in many parts of the world. Studies from the UK Prospective Diabetes Study and the Kumamoto study groups have documented that good metabolic control prevents or delays the development of late diabetic complications in patients with type 2 diabetes.[1–4] In type 2 diabetes, progressive β-cell failure is seen. Thus, lifestyle changes and oral antidiabetic drugs often become inadequate in maintaining glycemic control, and insulin treatment will be required.[5–8]

One way of introducing insulin treatment in patients with type 2 diabetes is to maintain oral antidiabetic treatment and inject intermediate-acting neutral protamine Hagedorn (NPH) insulin as a supplement at bedtime to cover the insulin need during nighttimes and in the morning hours.[9,10] Previous studies have shown that this mode of treatment may improve overall metabolic homeostasis with minor weight gain compared to insulin supplementation during the daytime.[11,12] A drawback of subcutaneous NPH insulin injection is, however, that plasma insulin peak levels are obtained approximately 5–7 hours after injection. Fluctuating plasma insulin levels throughout the night may result in nocturnal hypo- or hyperglycemia.[13] Alternatively, a long-acting insulin analogue can be administered once daily to cover day- and nighttimes. However, a drawback of the available long-acting insulin analogues for subcutaneous injection, insulin glargine and insulin detemir, could be that they still possess some peak effect and/or may not cover 24-hour insulin requirements.[14–17] Another drawback is the profound intra- and interindividual variations in the absorption of NPH insulin as well as the long-acting insulin analogues, which also could lead to hypo- and hyperglycemia.[16,18–20] Although we acknowledge that the new long-acting insulin analogues do produce improved insulin profiles compared to NPH insulin,[21] our hypothesis is that basal insulin supply still can be optimized. We believe that a constant delivery, as achieved by a constant subcutaneous infusion of a rapid-acting insulin analogue, may solve the mentioned drawbacks.[22]

Today, insulin dose titration in patients with type 2 diabetes is carried out in the same manner as in patients with type 1 diabetes, i.e., on a unit-by-unit basis. However, titration of insulin dose in type 2 diabetes may be simpler because of preserved endogenous insulin secretion. In fact, in an experimental pilot study,[23] we demonstrated that only a few predetermined insulin infusion levels overnight seemed necessary to obtain sufficient fasting plasma glucose (FPG) control in patients with type 2 diabetes who obtained insufficient glycemic control on oral antidiabetic drugs. Therefore, we anticipated a very limited dose range and used a fixed dose.

The intention of the present experimental study was to theoretically optimize basal subcutaneous insulin treatment by a *simple* standard regimen providing theoretically optimal constant basal subcutaneous insulin supplies for patients with type 2 diabetes. As a model for this delivery we used a pump system. Thus, we evaluated the effect of constant subcutaneous insulin infusion (CSII) at a fixed dose rate of 1.5 IU/h for 8 hours overnight and for 24 hours, respectively, on FPG and 2-hour postprandial plasma glucose (PPPG) in patients with type 2 diabetes treated with oral antidiabetic drugs. The study contributes to the theoretical knowledge for basal insulin supply.

Patients and Methods

Patients

A total of 10 patients with type 2 diabetes (all Caucasians, 2 women and 8 men) participated. Their baseline characteristics (at screening within 2 weeks before the first treatment period) are shown in **Table 1**. Inclusion criteria were age 18–75 years, body mass index of 23–38 kg/m^2, and diagnosed with type 2 diabetes at least 1 year before study start. The patients should be treated with two oral antidiabetic agents, metformin and sulfonylurea/repaglinide, without having achieved optimal metabolic control (FPG between 144 and 270 mg/dl, HbA1c above 7.0%). The doses of oral agents corresponded to local guidelines and individual patient tolerance. The local guideline, regarding treatment with metformin, recommended a dose of 1500–3000 mg/day. If the patients did not tolerate this dose, they were treated with a second oral antidiabetic drug instead of the maximal metformin dose (**Table 1**). All of the patients had metformin as tablet Orabet®. Metformin in the form of sustained release metformin is not available in Denmark.

Exclusion criteria included previous treatment with insulin, any systemic concomitant medication influencing glycemic control, hypoglycemic unawareness, reduced renal capacity (S-creatinine ≥150 μmol/liter),

Table 1.
Mean ± SD or Median (Range) Corresponding to Baseline Characteristics for the 10 Patients in the Study

Age (year)	62.2 ± 7.5
Body mass index (kg/m^2)	32.1 ± 3.1
Duration of type 2 diabetes (years)	7.5 (2–22)
FPG (mg/dl)	196.2 ± 48.6
HbA1c (%)	8.7 ± 1.4
Systolic blood pressure (mm Hg)	155.0 ± 12.9
Diastolic blood pressure (mm Hg)	82.5 ± 5.9
Total cholesterol (mmol/liter)	5.1 ± 0.8
Daily dose of oral antidiabetic agent (mg)	
• Metformin	1250 (500–2500)
• Gliclazide	160 (160–190)
• Glibenclamide	10.5
• Glimepiride	3 (2–4)
• Tolbutamide	1000
• Glipizide	10
• Repaglinide	6

reduced hepatic capacity (alanine aminotransferase or alkaline phosphatase ≥2 times above the upper local reference limit), severe cardiac insufficiency or unstable angina/myocardial infarction within the last 12 months, uncontrolled difficult hypertension, planned or existing pregnancy, and any other clinically significant concomitant disorders.

Study Design

The trial was a randomized, open-label, two-period crossover study performed at the Department of Endocrinology and Diabetes, Aarhus University Hospital, Denmark. The trial protocol was approved by the local ethical committee and the Danish Medical Agency and was conducted in accordance with the Declaration of Helsinki 2000 by the principles of good clinical practice. Written informed consent from all the patients was obtained before enrollment in the study.

The study consisted of 1 initial control day followed by two crossover treatment periods. The treatment periods, A and B, each lasted 3 days and were separated by a 2-week washout period. According to our previous pilot study,[23] the most optimal dose for 8 hours of overnight insulin infusion in similar patients was 1.5–2.0 IU/h. Therefore, as we chose the same rate in the present study for both treatment periods we decided to use the lower rate limit for safety reasons. All patients in the present study started their treatment periods with period A, after they had been randomized to receive an insulin infusion at a rate of 1.5 IU/h either for 8 hours overnight or for 24 hours.

The patients arrived at the hospital in the evening of the control day. The following evening at approximately 10 PM, in period A, a Medtronic MiniMed 508 insulin pump (Medtronic, Copenhagen, Denmark) was connected by an Unomedical™ basic infusion set (Unomedical, Roskilde, Denmark) to the abdominal subcutis for the infusion of insulin aspart (NovoRapid®, Novo Nordisk, Bagsvaerd, Denmark).[24] During the night, plasma glucose (PG) and circulating levels of insulin were measured every second hour. Two hours before breakfast, at approximately 6 AM, FPG was measured. During the day, similar profiles were recorded immediately before lunch and dinner, 2 hours after the three main meals, and at bedtime at approximately 10 PM. A bedside Medisense Precision Xtra blood glucose meter (Abbott Laboratories, Gentofte, Denmark) also measured PG for safety reasons. The three standardized main meals were served at approximate 8 AM, 12 noon, and 6 PM, and three standardized small snacks were provided late in the morning, in the afternoon, and in the evening. In total, women received approximately 8000 kJ/day (1900 kcal/day) and men approximately 10,000 kJ/day (2400 kcal/day), but this was adjusted according to individual requirements and habits. The exact same pattern was repeated the next days, and the patient completed period A when the third treatment day was fulfilled. Period B was carried out in the same way as period A, however, with the alternative treatment. Throughout the study the patients received their usual oral antidiabetic treatment and concomitant medication.

Low PG readings, defined as no symptoms and PG <63.0 and ≥55.8 mg/dl, were recorded to indicate a possible distribution. Hypoglycemic episodes were defined as (1) symptoms only if PG ≥55.8 mg/dl, (2) minor if PG <55.8 mg/dl and the patient was able to treat the episode, or (3) major if PG <55.8 mg/dl and another person had to treat the patient with intravenous glucose.

Measurements

Plasma glucose was measured by the glucose oxidase method on a Beckman glucose analyzer (Beckman Instruments, Palo Alto, CA).[25] Serum human endogenous insulin was measured by an enzyme-linked immunosorbent assay test (human insulin ELISA) (Dako Norden, Glostrup, Denmark).[26] Serum insulin aspart was measured by a sandwich time-resolved immunofluorometric assay as described by Andersen and colleagues,[27] except that the detecting antibody was europium labeled (Research Laboratory for Department of Endocrinology and Diabetes, Aarhus

University Hospital, Aarhus, Denmark). No detectable cross-reactivity was found between human insulin and insulin aspart.[27] The detection limit in serum for human insulin concentrations was 12.0 pmol/liter and for serum insulin aspart was 15.6 pmol/liter. Detection limits for the different insulin types were defined as two standard deviations above zero. In statistical analyses, values below the detection limits for human insulin and insulin aspart were set to zero.

Statistical Analysis

A total of 10 patients were needed in this study to detect a FPG difference of 45.0 mg/dl between the control day and CSII treatments with 80% of power, a 5% (two-sided α) significance level, and a standard deviation of the FPG difference of 45.0 mg/dl. Tests for period and carryover effects were nonsignificant. Data are presented as mean ± SEM. An analysis of variance (ANOVA) for repeated measurements by means of a mixed effect model was performed to compare the control day, 8-hour, and 24-hour plasma glucose values (**Table 2**). Post-hoc pair-wise comparisons of the FPG and PPPG values were also performed by means of the mixed effect model. The trapezoidal method was used to calculate the area under the curve (AUC) of the profiles for plasma glucose, endogenous insulin, and insulin aspart (**Figure 1**). AUC profiles were compared by an ANOVA for repeated measurements. p values < 0.05 were considered statistically significant.

Results

Subjects

All 10 patients with type 2 diabetes completed the study.

Table 2.
Mean Control and Differences ± SEM in FPG and 2-Hour PPPG Values after Three Main Meals among Control Day (C), 8-Hour Overnight (8 h), and 24-Hour (24 h) Subcutaneous Insulin Infusions [a]

	C, mean ± SEM (mg/dl)	ΔC vs 8 h, mean ± SEM (mg/dl)	ΔC vs 24 h, mean ± SEM (mg/dl)	Δ8 h vs 24 h, mean ± SEM (mg/dl)
FPG	163.6 ± 12.8	59.0 ± 10.1**	68.9 ± 10.1**	9.9 ± 7.2^{ns}
PPPG, breakfast	281.2 ± 12.8	57.8 ± 10.6**	86.4 ± 10.1**	28.8 ± 8.1**
PPPG, lunch	185.0 ± 12.8	13.5 ± 10.6^{ns}	43.9 ± 10.3**	30.6 ± 8.1**
PPPG, dinner	214.0 ± 12.8	13.3 ± 10.6^{ns}	48.4 ± 10.1**	35.1 ± 7.9**

[a] Insulin therapy resulted in lower plasma glucose levels than on control day.
**$p < 0.01$; ns, nonsignificant ($p > 0.05$).

Fasting Plasma Glucose and Postprandial Plasma Glucose

Table 2 shows that compared to the control day without insulin treatment, 8 hours of overnight insulin infusion for 3 days significantly reduced FPG and PPPG after breakfast, whereas 24 hours of infusion for 3 days significantly reduced FPG and PPPG values after breakfast, as well as after lunch and dinner. Furthermore, compared to 8 hours of overnight insulin infusion, 24 hours of infusion significantly improved all three PPPG values.

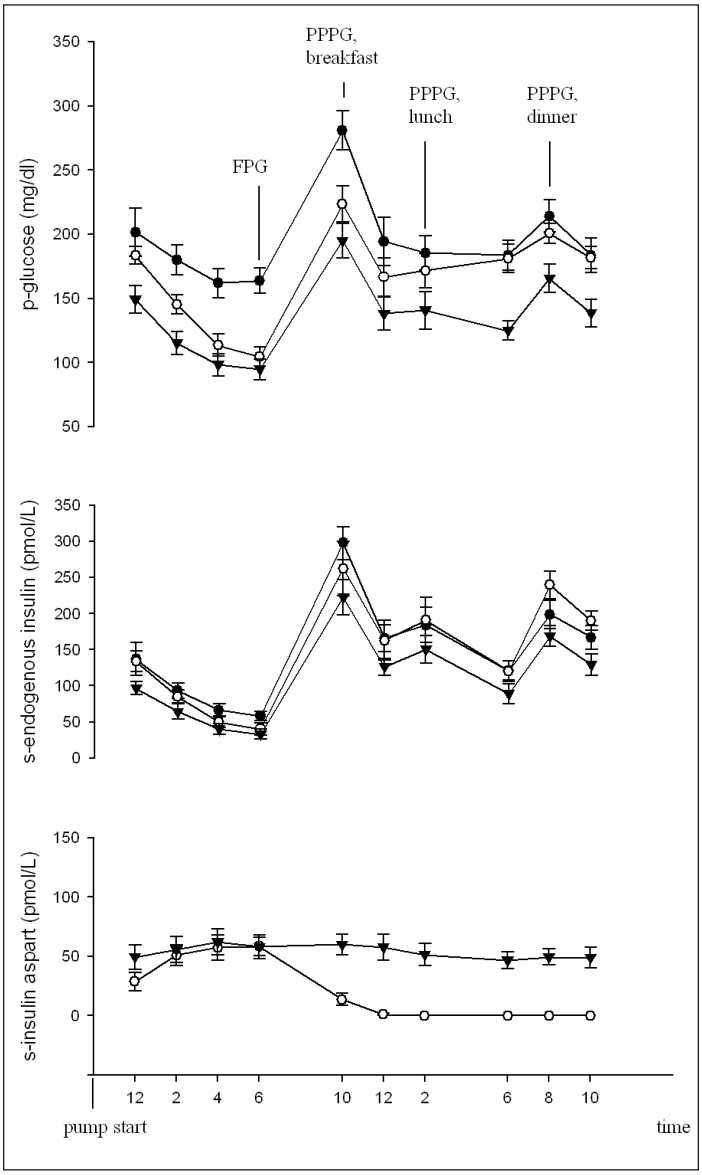

Figure 1. Mean ± SEM glucose and insulin profiles for control day (black circle), 8-hour overnight (white circles), and 24-hour (black triangle) subcutaneous insulin infusions. Top panel illustrates the plasma glucose profiles (mg/dl). FPG and 2-hour PPPG after the three main meals are marked. Middle and lower panels demonstrate the corresponding serum profiles of endogenous insulin and insulin aspart (pmol/liter), respectively, using the same symbols for the three different situations as for plasma glucose.

The 8-hour overnight and 24-hour treatment effects were similar for FPG, and for both treatments the effect was most pronounced for FPG and PPPG after breakfast. Moreover, compared to the control day, the 8-hour overnight treatment effect seen around breakfast gradually waned during the rest of the day, and the PPPG values after lunch and dinner were not significantly lowered.

Plasma Glucose and Serum Insulin Profiles

Figure 1 demonstrates the three situations: a control day without insulin treatment, 8 hours of overnight insulin infusion, and 24 hours of insulin infusion. As day-to-day effects for PG values were not significant ($p > 0.05$), each of the treatment graphs illustrates the mean of 3 consecutive treatment days. Infusions were initiated at approximately 10 PM, and time intervals represent measurements from 2 hours after start of the pump (approximately 12 midnight) to approximately 10 PM the following day.

As evident from the calculated AUC plasma glucose levels, the control day curve was higher than those obtained with both insulin infusion regimens ($p < 0.05$), and the 8-hour overnight insulin infusion curve was higher than the 24-hour infusion curve ($p < 0.01$). **Figure 1** also illustrates fluctuations in endogenous insulin and insulin aspart profiles. No difference could be found between endogenous insulin AUC during the control day and 8 hours of overnight infusion ($p > 0.05$). In contrast, compared to the control day and the 8-hour overnight infusion curves, endogenous insulin was suppressed during the 24-hour insulin infusion days ($p < 0.01$). Excursions in endogenous insulin could still be observed in response to meals. Moreover, during 24-hour insulin infusion, the levels of insulin aspart tended to be constant.

Safety

Two patients had low PG readings with no symptoms during the two treatment periods of 3 days. One patient had one reading, whereas the other patient had three readings. Only one hypoglycemic episode with a PG value of 52.2 mg/dl was measured, and this patient only experienced mild symptoms (sweating). The low PG readings were distributed with one recording during 8 hours of overnight insulin infusion and three recordings during 24 hours of infusion. All low PG readings occurred during the night. The one hypoglycemic episode occurred during the 8-hour overnight infusion. No major hypoglycemic events occurred during the trial.

Discussion

The intention of this experimental study was to evaluate the impact of a simple standard regimen providing a theoretically optimal constant basal subcutaneous insulin supply for 8 hours overnight compared to 24 hours in patients with type 2 diabetes. For this purpose insulin pumps were used.

Compared with the control day, 8 hours of overnight as well as 24 hours of insulin infusion exerted a profound beneficial effect on FPG and PPPG after breakfast with a reduction in glucose ranging from 57.8 to 86.4 mg/dl. Further, compared to the 8-hour overnight infusion, the 24-hour infusion provided an additional reduction in PPPG of 28.8–35.1 mg/dl after all three meals (**Table 2**).

A fixed dose of 1.5 IU/h was used in all patients in this study. This dose resulted in clinically significant PG reductions without inducing safety concerns in any patients. We wanted to examine whether an 8-hour overnight approach would be sufficient, but in general it did not seem to be the case. Moreover, despite the additional beneficial effect of 24 hours of infusion compared to 8 hours of overnight infusion, results indicate a need for bolus insulin at breakfast and maybe also at dinner (**Figure 1**). In our previous pilot study with overnight CSII,[23] the most optimal dose for reducing FPG seemed to be an insulin infusion rate of 1.5–2.0 IU/h. This may indicate that a higher fixed dose rate would have been beneficial and may have overcome the need for extra bolus insulin. Moreover, the duration of each treatment period was short, which could have influenced the results of the study.

The superior effect of 24 hours of insulin infusion related to a larger total insulin dose per day as well as to the longer duration of insulin infusion. The same total insulin dose per day was not chosen for the two insulin infusion regimes, as this could have resulted in hyper- or hypoglycemia due to either a too low dose for 24 hours of infusion or a too high dose for 8 hours of overnight infusion.

In these patients with type 2 diabetes who had secondary failure to oral antidiabetic drug treatment, a significant endogenous insulin production was still present (**Figure 1**), as also reported in other studies.[7,28] During the 24-hour infusion the infused insulin aspart resulted in a reduction in serum levels of endogenous insulin (**Figure 1**). This supports the finding that some patients with type 2 diabetes can probably be treated successfully

with just a limited number of insulin delivery rates due to suppression of the endogenous insulin release with an insulin dose that partly substitutes endogenous insulin.

The trial also illustrated that plasma levels of endogenous insulin can be distinguished from those of an exogenous insulin analogue. This allowed an evaluation of preserved β-cell function during insulin analogue treatment in patients with type 2 diabetes in a relatively simple setup. In the present study, endogenous insulin, which was suppressed during the 24-hour infusion in an almost parallel order, during 3 consecutive days, was unable to prevent elevated PPPG levels (**Figure 1**). Whether an exogenous insulin supply will serve to spare β cells in the long run and be able to respond more appropriately to postprandial glycemia needs to be clarified. However, evidence suggests that optimized glycemic control improves β-cell function in patients with type 2 diabetes.[29,30]

In the present study, as well as in another study,[31] 24 hours of CSII seems to result in a true constant serum insulin profile (**Figure 1**). The responding theoretically beneficial impact on glucose levels could speak in favor of regimens providing an almost constant insulin supply.[21,22,32–34] The new long-acting insulin analogues to some extent produce similar effects, but they still have problems with day-to-day variation in absorption and peak plasma concentrations.[16] Thus, we believe there is a need for further improvement of subcutaneous delivery by developing new long-acting insulin analogue preparations or by further development of smaller, more safe, and handy insulin pumps, perhaps as simple insulin patches with a few different doses.

The present study was exploratory, and a randomized controlled longer term study of efficacy and safety of equal doses of a long-acting insulin analogue versus 24 hours of insulin pump treatment in a larger group of patients with type 2 diabetes will be our next approach.

In conclusion, CSII with a rapid-acting insulin analogue at a *fixed rate* of 1.5 IU/h, either overnight or for 24 hours, improved glycemic control without safety concerns in patients with type 2 diabetes who had secondary failure to oral antidiabetic drugs. The effect on FPG was similar for both treatments, whereas the effect on PPPG was superior when insulin was infused during the entire 24 hours.

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Disclosures:

T. Parkner is the recipient of unrestricted grants for research from Novo Nordisk. T. Laursen has received consultant fees from Novo Nordisk and Novartis. H.F. Thomsen is a former employee at Novo Nordisk. C. Jørgensen and J.S. Smedegaard are employed and have shares in NovoNordisk. T. Lauritzen has received lecture and consultant fees from NovoNordisk and Merck Sharp & Dohme and is the recipient of unrestricted funds for research from Novo Nordisk, Pfizer, AstraZeneca, GlaxoSmithKline, and Servier. J.S. Christiansen has received lecture and consultant fees from Novo Nordisk, Novartis, and Roche and is the recipient of unrestricted funds for research from NovoNordisk, Pfizer, and Roche.

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