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ORIGINAL ARTICLES

Explorative Study of Pharmacokinetics and Pharmacodynamics after Change in Basal Insulin Infusion Rate

Charlotte A. Ihlo, M.D.,[1] Torsten Lauritzen, M.D., Dr.Med.Sci.,[2] Jeppe Sturis, Ph.D.,[3] Ole Skyggebjerg, M.Sc., Ph.D.,[4] Jens S. Christiansen, M.D., FRCPI, Dr.Med.Sci.,[1] and Torben Laursen, M.D., Ph.D., Dr.Med.Sci.[5]

Abstract

Background:

The use of insulin pumps is rapidly increasing and new, technologically more advanced pumps are continuously being developed. It is of interest to assess the clinical relevance of the many technical features of these pumps, e.g., the effect on pharmacokinetics and pharmacodynamics with change in infusion rate.

Method:

The aim of this study was to explore the sequence of pharmacokinetic and pharmacodynamic changes after dose doubling of the basal insulin infusion rate with subcutaneous bolus insulin injections once an hour, continuous subcutaneous insulin infusion, and continuous intravenous insulin infusion. Ten type 1 diabetes mellitus patients were included. The insulin doses were calculated based on the habitual insulin doses. The study was designed as an open-labeled, single-center, randomized, crossover exploratory trial.

Results:

Dose doubling of the basal insulin infusion rate with the three different administration protocols did not result in any clinically relevant differences in the time courses of the pharmacokinetic and pharmacodynamic parameters. With all three administration protocols, we observed a time interval of more than 6 hours before a new steady state of insulin was achieved.

Conclusions:

Our results indicate that frequent changes in basal subcutaneous insulin infusion rates are not of significant clinical relevance on a 24-hour basis. Regarding technological features of subcutaneous insulin pumps, no discernable advantages of increasing pump stroke frequency were found. This indicates that pump stroke frequency sophistication might not be of clinical relevance in pumps used for basal subcutaneous insulin infusion.

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Author Affiliations: [1]Department of Endocrinology M, Aarhus University Hospital, Aarhus C, Denmark; [2]Department of General Medicine, Institute of Public Health, Aarhus University, Aarhus C, Denmark; [3]Department of Insulin, Pharmacology, Histology and Delivery, Novo Nordisk A/S, Maeloev, Denmark; [4]Insulin Pharmacology, Histology and Delivery, Novo Nordisk A/S, Maeloev, Denmark and [5]Department of Pharmacology, Aarhus University, Aarhus C, Denmark

Abbreviations: (ANOVA) analysis of variance, (AUC) area under the curve, (CIII) continuous intravenous insulin infusion, (cl) clearance, (CSII) continuous subcutaneous insulin infusion, (CV) coefficient of variation, (GIR) glucose infusion rate, (HbA1c) hemoglobin A1c, (IAsp) insulin aspart, (IU) international unit, (IV) intravenous, (PG) plasma glucose, (s) serum, (SBII) subcutaneous bolus insulin injection, (SC) subcutaneous, (SD) standard deviation, (SE) standard error (ss) steady state, ($t_{1/2}$) terminal half life in blood, ($t_{50\%}$) terminal half life of insulin absorption, (T1DM) type 1 diabetes mellitus, (U-HCG) urinary human chorionic gonadotropin

Keywords: insulin aspart, insulin pump therapy, steady state

Corresponding Author: Charlotte A. Ihlo, M.D., Department of Endocrinology M, Aarhus Sygehus, NBG, Aarhus University Hospital, Noerrebrogade 44, Building 2, DK-8000 Aarhus C, Denmark; email address charlotte.ihlo@dadlnet.dk

Introduction

The aim of insulin therapy is to achieve near normoglycemia. Intensive insulin therapy aims to imitate the complex kinetics of physiological insulin secretion by subcutaneous (SC) insulin injections. Continuous subcutaneous insulin infusion (CSII) seeks to mimic endogenous insulin secretion by delivering rapid-acting insulin as a basal infusion rate and additional bolus delivery with meals.

With CSII, the basal rate is often changed several times on a 24-hour basis in a specific pattern according to individual needs.[1]

Several studies have characterized the time-action profile of insulin aspart (IAsp) administration SC. A terminal half life of insulin absorption ($t_{50\%}$) of approximately 90 min (0.1 IU/kg) (healthy males),[2] 76 min (0.1 IU/kg) (healthy subjects),[3] and 122 min (0.15 IU/kg) [patients with type 1 diabetes mellitus (T1DM)][4] have been reported after SC bolus injections. The $t_{50\%}$ after SC administration is dependent on the terminal rate of absorption from the subcutaneous depot. Mean total plasma clearance has been found to be comparable after SC and intravenous (IV) administration (1.24 liter·h^{-1}·kg^{-1} and 1.22 ± 0.32 liter·h^{-1}·kg^{-1}, respectively).[5,6]

Clearance is defined as the volume of plasma containing the amount of substance that is removed in unit time. For a single compartment model, a continuous infusion can be regarded as the extreme of a repeated dose schedule. In this case, the plasma concentration increases until a steady state concentration (C_{ss}) is reached, where the rate of infusion (R) equals the rate of elimination (cl):

$$C_{ss} = R/cl \quad (1)$$

The drug concentration approaches this steady state value exponentially.

Repeated injections give a more complicated pattern. The smaller and more frequent the doses, the more closely the situation approaches that of continuous infusion, and the smaller the variation of the concentration. In practice, a steady state is effectively achieved after four to five $t_{50\%}$. Thus, the time to steady state of IAsp with CSII has been estimated to be 228–456 min ($t_{50\%}$ = 76 min) in healthy subjects and 488–610 min in T1DM patients. A study with insulin lispro has found that steady state was achieved after 120 min with infusion rates of 0.5 and 1.0 IU/h, whereas no steady state was achieved with an infusion rate of 2.0 IU/h within a 4-hour clamp period.[7]

A study with human insulin has found that steady state was achieved after 60–90 min with continuous intravenous insulin infusion (CIII) and 6–8 h with CSII (2.4 IU/h).[8]

In this study, we aimed to evaluate the sequence of pharmacokinetic [serum insulin aspart (s-IAsp)] (primary endpoints) and pharmacodynamic [plasma glucose (PG) and glucose infusion rate (GIR)] (secondary endpoints) changes after dose doubling of basal insulin infusion rates with SC bolus insulin injection (SBII), CSII, and CIII. We evaluated time to achievement of a new steady state after dose doubling of IAsp and clearance of s-IAsp.

Methods

The protocol was approved by the Central Denmark Region Committees on Biomedical Research Ethics, the Danish Medicines Agency, and Good Clinical Practice Unit at Aarhus University Hospital, Aarhus, Denmark, and was in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Subjects

A total of 13 T1DM patients (01–13) were included in the study. The protocol for the main study was based on results from a pilot study including 3 patients (01–03). The patients were selected from a population of insulin pump users at the Department of Endocrinology, Aarhus University Hospital. The pilot study will not be further described here.

Study Design

We aimed to evaluate the sequence of pharmacokinetic (s-IAsp) (primary endpoints) and pharmacodynamic (PG and GIR) (secondary endpoints) changes after dose doubling of basal insulin infusion rates with SBII, CSII, and CIII.

The study was designed as an open-labeled, single-center, randomized, crossover exploratory trial.

The patients were admitted at 18:00 at the Department of Endocrinology, Aarhus University Hospital. Infusion site, insulin pump, and insulin pump utensils were changed

at admittance. The pump catheter for SC delivery was inserted in the abdomen. The pump catheter for IV delivery was inserted in an upper extremity vein. Prior to study start, the catheter was primed.

18:00–08:00. A basal rate of IAsp was administered from the pump.

18:00–00:00. Additional IAsp boluses were administered with meals.

00:00–18:00. Fasting.

08:00–18:00. The basal rate was increased by 100% in order to detect potential changes in pharmacokinetic and pharmacodynamic parameters.

18:00. The trial was completed, a meal was served, and the habitual insulin pump settings were restored. All patients were discharged within 2 hours of study completion.

An indwelling catheter was placed in an antecubital vein for glucose infusion. In the contralateral antecubital vein, a catheter for blood sampling was placed.

IAsp Infusion Protocol

SBII protocol. 18.00–08.00: 50% of the habitual 24 h insulin need per 24 h = basal rate (per hour) SC; 08.00–18.00: bolus administration once an hour. The basal rate was increased by 100% and administered as a single dose once an hour SC.

CSII protocol. 18.00–08.00: 50% of the habitual 24 h insulin need per 24 h = basal rate (per hour) SC; 08.00–18.00: 100% increase of the basal infusion rate SC.

CIII protocol. 18.00–08.00: 50% of the habitual 24 h insulin need per 24 h = basal rate (per hour) IV; 08.00–18.00: 100% increase of the basal infusion rate IV.

Habitual IAsp dose. 0.023 ± 0.008 IU/kg per 24 hours [mean ± standard deviation (SD)], dose range: 0.012–0.03 IU/kg per 24 hours.

The calculated doses of IAsp were adjusted to possible insulin pump administration settings, and each patient received identical doses in all three study protocols. See **Table 1**.

Table 1.
Calculated Insulin Aspart Doses/Dose Range (Mean ± SD) (IU/h) and Weight Adjusted Calculated Insulin Aspart Doses (Mean ± SD)/Dose Range ($IU \cdot kg^{-1} \cdot h^{-1}$)

	Calculated insulin aspart doses/dose range (mean ± SD) (IU/h)	Weight adjusted calculated insulin aspart doses (mean ± SD)/dose range ($IU \cdot kg^{-1} \cdot h^{-1}$)
18:00–08:00	0.8 ± 0.3 / 0.4–1.25	0.011 ± 0.003 / 0.006–0.014
08:00–18:00	1.6 ± 0.6 / 0.8–2.5	0.022 ± 0.006 / 0.013–0.030

Insulin Pump Characteristics

Pump stroke frequency. 18.00–08.00 (SBII/CSII/CIII): 15.9 ± 5.4 strokes/h; 08.00–18.00 (CSII/CIII) 32.4 ± 11.0 strokes/h; 08.00–18.00: duration of SBII once an hour, 65.2 ± 22.0 s (mean ± SD).

Biochemistry. Blood sampling for serum s-IAsp and PG: 18:00–08:00 every hour, 08:00–12:00 every 20 min, and 12:00–18:00 every 10 min. The interval between blood sampling was reduced to 10 min in the period when steady-state IAsp was expected to be reached in all three study protocols.

Additional biochemistry at inclusion. C-peptide, hemoglobin A1c (HbA1c), hemoglobin, leucocytes, thrombocytes, Na+, K+, albumin, carbamide, creatinine, urinary human chorionic gonadotropin (U-HCG) (fertile women), electrocardiogram. U-HCG was measured prior to each study day in all fertile women.

A manual euglycemic clamp aiming at PG in the range of 5.0–8.0 mM was performed. This range was chosen to mimic the clinical situation as closely as possible. The clamp was performed throughout each study period of 24 h.

Assays

Glucose. PG was measured by ACCU-CHEK® Inform (Roche A/S, Maeloev, Denmark).

IAsp. IAsp is an analog of human insulin in which proline at position 28 of the β-chain is replaced by aspartic acid. U 100 IAsp was used.[9]

s-IAsp. Luminescent oxygen channelling immunoassay (LOCI™) was performed at Novo Nordisk A/S (Maeloev, Denmark) by a trained laboratory technician.

The analytical precision and accuracy of the assay were found: coefficient of variation (CV) of mean s-IAsp in pM: 3.42–10.9%; interassay CV: 1.58–7.1%; intraassay CV: 3.71–11.7%; accuracy: 4.02–13.9%.[10]

Insulin pump. Paradigm® 515 insulin pump (Medtronic MiniMed, Copenhagen, Denmark). Pump specifications: increment resolution: 0.5 µl/stroke; insulin delivery per stroke: 0.05 IU; time interval between strokes: 2 seconds.

Infusion sets. Paradigm Silhouette® infusion sets, 17 mm (60 cm) (MMT-380 A) (Medtronic MiniMed, Copenhagen, Denmark).

Paradigm® reservoirs, 3 ml, were used (MMT-332) (Medtronic MiniMed, Copenhagen, Denmark).

Statistical Analysis

The statistical analyses were performed with SAS® 9.1 (SAS Institute, Inc., Cary, NC) and APL*PLUS, (STSC Inc., Rockville, MD). As the study was explorative, power calculations were not performed. Variables are expressed as mean values with SEM (standard error of the mean) or SD, and as median and range.

Nonmodel-Based Analysis

Evaluation of steady state. Visual evaluation of time to steady state was performed, and Spearman's rank correlation test was used to test for monotony in order to quantitatively evaluate whether steady state was achieved.

Evaluation of time to steady state. We evaluated time to steady state with the following three methods:

1. Spearman's rank correlation (r_s) with successive exclusion of data after dose doubling;
2. Spearman's rank correlation (r_s) with a chosen trend index of 2 hours after dose doubling;
3. Mann-Whitney U test with calculation of slope trends in 2-hour intervals after dose doubling.

In the nonmodel-based analysis, clearance was calculated directly from the definition

$$cl = R/\text{s-IAsp} \quad (2)$$

R is the dose in IU administered per hour and kg body weight and s-IAsp is the steady state concentration of s-IAsp, i.e., the average of s-IAsp measured in the time interval 22–24 hours. Per definition, 1 IU IAsp equals 6 nmol and cl is usually expressed as $ml \cdot min^{-1} \cdot kg^{-1}$, therefore the following conversion was used:

$$cl = (6 \cdot R)/(10^{-3} \cdot 60 \cdot 10^{-3} \cdot \text{s-IAsp}) = 10^5 \cdot \text{R/s-IAsp} \quad (3)$$

The area under the curve (AUC) was calculated using the trapezoid rule. A two-way, repeated measurement analysis of variance (ANOVA) was applied for comparison of (AUC/h)/(ΔAUC/h), and AUC/ΔAUC; $p < .05$ was considered to be significant.

Model-Based Analysis

Assuming first order kinetics, the following model was used:

$$X(t) = \alpha + \beta[1 - \exp(-\gamma t)] \quad (4)$$

$X(t)$ is s-IAsp at the time t (measured in hours from 08:00), α is s-IAsp at 08:00, β is the asymptotic increase of s-IAsp, γt is the rate constant of the s-IAsp increase, which, assuming first-order kinetics, is proportional to the disappearance rate from the SC depot with SC administration. The rapid clearance from the blood results in a quasi-steady-state where the rate of insulin administration to the blood (= disappearance from the SC depot) is proportional to s-IAsp.

The rate constant of s-IAsp increase (γ) showed an extreme variation with both SBII and CSII. Because of this large variation and negative values, γ is not considered usable for calculation of $t_{50\%}$ ($t_{50\%} = \ln 2/\gamma$).

The variation of the s-IAsp (α) and asymptotic increase of s-IAsp (β) was less pronounced. With α + β equaling s-IAsp (steady state) clearance with SBII and CSII was calculated as

$$cl = (6 \cdot R)/(10^{-3} \cdot 60 \cdot 10^{-3} \cdot \text{s-IAsp}) = 10^5 \cdot R/(\alpha + \beta) \quad (5)$$

Results

Ten patients (04–13) were included in and fulfilled the main study. Age: 41.2 ± 8.1 years, body mass index: 24.1 ± 3.9 kg/m^2, HbA1c: 7.2 ± 0.8% per 55 mmol/mol, duration of T1DM: 22.1 ± 11.8 years, duration of CSII: 5.3 ± 6.3 years, habitual IAsp dose: 0.023 ± 0.008 IU/kg per 24 h (mean ± SD), and dose range: 0.012–0.03 IU/kg per 24 h.

Pharmacokinetics

Figure 1 shows the individual and median s-IAsp with SBII, CSII, and CIII in the time interval from 00:00–18:00

(fasting period). From 00:00, s-IAsp gradually declines with SBII and CSII, whereas the decline visually appears to be steeper with CIII. Dose doubling at 08:00 is followed by an increasing mean s-IAsp with all three administration protocols. Visually, a gradual increase in mean s-IAsp with CSII is observed, whereas a peak of s-IAsp is observed in close proximity to dose doubling with SBII and CIII (most pronounced with CIII).

Nonmodel-Based Analysis

Visually, steady-state s-IAsp was achieved after approximately 7 hours after dose doubling with all three administration protocols.

With Spearman's rank correlation test for monotony, the visual impression of steady state was verified after 7 hours with SBII and CIII, and after 8 hours with CSII. With the application of Spearman's rank correlation (r_s) with successive exclusion of data after dose doubling or with a chosen trend index of 2 hours, and a Mann-Whitney U test with calculation of slope trends in intervals of 2 hours, time to steady state could not be determined. For the Spearman's rank correlation tests, this might be due to the relatively high variations in r_s (data not shown).

The increases in s-IAsp after dose doubling were compared. Estimated means ± standard error (SE) and p values of $AUC_{14–15\ h}$, $AUC_{14–17\ h}$, $AUC_{14–20\ h}$, $AUC_{14–24\ h}$, $\Delta AUC_{14–15\ h}$, $\Delta AUC_{14–17\ h}$, $\Delta AUC_{14–20\ h}$, and $\Delta AUC_{14–24\ h}$ of s-IAsp were calculated. No significant differences of AUC and ΔAUC between SBII, CSII, and CIII were found. Estimation of $AUC_{14–15\ h}/h$, $AUC_{14–17\ h}/h$, $AUC_{14–20\ h}/h$, $AUC_{14–24\ h}/h$, $\Delta AUC_{14–15\ h}/h$, $\Delta AUC_{14–17\ h}/h$, $\Delta AUC_{14–20\ h}/h$,

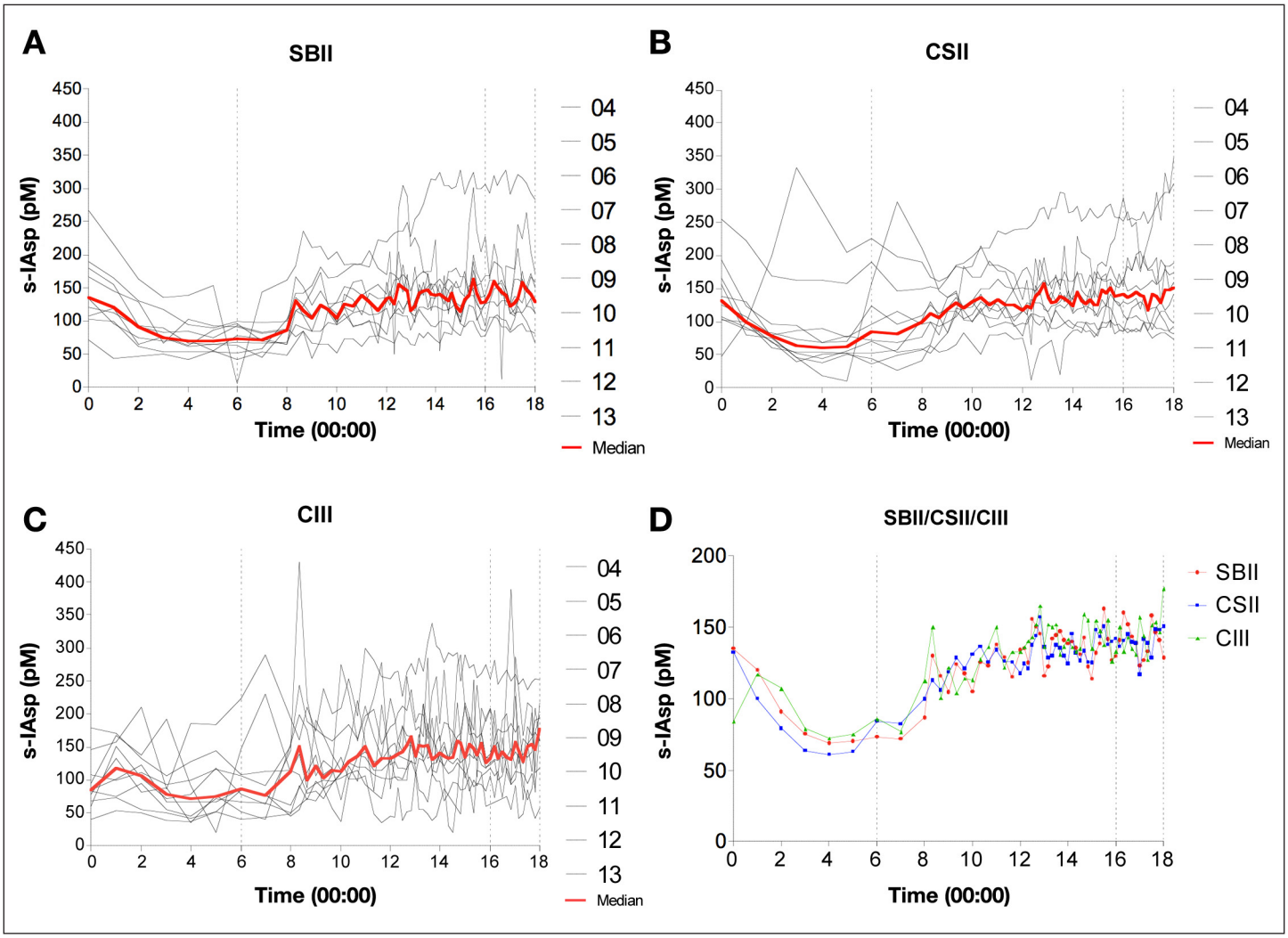

Figure 1. Individual and median serum insulin aspart (s-IAsp) with SBII, CSII, and CIII. Upper left panel: SBII, upper right panel: CSII, lower left panel: CIII, lower right panel: mean SBII, CSII, and CIII. X-axis: absolute time of the day clock. 00:00: start of fasting. 06:00: dose doubling of IAsp. 16:00–18:00: defined steady state.

and $\Delta AUC_{14–24\ h}$/h of s-IAsp showed a monotone increase of AUC/h and ΔAUC/h with all three administration protocols. A lower but nonsignificant increase with CIII compared to SBII and CSII was found. Assuming linear kinetics, AUC and ΔAUC for the respective time intervals should be proportional in the relation 2:1. This was only found to be the case with SBII.

A nonmodel-based estimation of clearance (see **Statistical Analysis**) was performed (data not shown).

Model-Based Analysis

A nonlinear regression analysis was applied for estimation of the model for s-IAsp variation after dose doubling with SBII and CSII. The obtained parameter values were highly variable (data not shown).

The individual values were calculated. The mean values (data not shown) were found to be similar to data presented in **Table 2**. No statistically significant differences between SBII, CSII, and CIII were found.

The model-based estimation of clearance ($ml \cdot min^{-1} \cdot kg^{-1}$) (see **Statistical Analysis**) based on achieved steady state 8 hours after dose doubling of IAsp with all three study protocols (Spearman's rank correlation test) are presented in **Table 2**. The first s-IAsp measurement is 20 minutes after dose doubling (4–10 $t_{50\%}$), where s-IAsp almost has reached an asymptotic level. Thus, CIII is considered to be a good approximation of a steady-state model. Thus, *cl* can be estimated as shown earlier using data obtained with CIII after 20 min. No significant differences of estimated clearances of s-IAsp with SBII, CSII, and CIII were found.

Pharmacodynamics

Figure 2 shows the individual and median PG with SBII, CSII, and CIII in the time interval from 00:00–18:00 (fasting period). Dose doubling of the IAsp at 08:00 is followed by a time interval of 2–3 h with declining PG to approximately 6 mM. At the end of the study, PG is approximately 7 mM.

Table 2.
Estimated Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$) Based on Steady State s-IAsp

Administration	Mean	SD	SEM	Median	Minimum	Maximum
SBII	15.8	4.4	1.4	16.5	4.2	20.1
CSII	17.2	6.3	2.0	18.2	4.7	27.4
CIII	16.5	5.9	1.9	15.9	5.1	26.8

The declines in PG after dose doubling were compared. Estimated means ± SE and *p* values of $AUC_{14–15\ h}$, $AUC_{14–17\ h}$, $AUC_{14–20\ h}$, $AUC_{14–24\ h}$, $\Delta AUC_{14–15\ h}$, $\Delta AUC_{14–17\ h}$, $\Delta AUC_{14–20\ h}$, and $\Delta AUC_{14–24\ h}$ of PG were calculated. No significant differences between SBII, and CSII, and CIII were found (data not shown).

Figure 3 shows the median GIR with SBII, CSII, and CIII in the time interval from 00:00–18:00 (fasting period). Following dose doubling, GIR increases to approximately 4 $mg \cdot min^{-1} \cdot kg^{-1}$ after 7 hours. The increases in GIR after dose doubling were compared. Estimated means ± SE and *p* values of $AUC_{14–15\ h}$, $AUC_{14–17\ h}$, $AUC_{14–20\ h}$, $AUC_{14–24\ h}$, $\Delta AUC_{14–15\ h}$, $\Delta AUC_{14–17\ h}$, $\Delta AUC_{14–20\ h}$, and $\Delta AUC_{14–24\ h}$ of GIR were calculated. No significant differences were found (data not shown).

Discussion

The gradual decrease in insulin with SBII and CSII between 00:00–08:00 is assumed to reflect a gradual emptying of the SC depot. This is in correspondence with previous studies where $t_{50\%}$ has been found to be approximately 90 min (healthy males),[2] 76 min (healthy subjects),[3] and 122 min (T1DM patients).[4] With CIII, the insulin decrease is steeper.

Visually, steady state was achieved after approximately 7 hours with all three administration protocols. With Spearman's rank correlation test for monotony, the visual impression of steady state was verified after 7 hours with SBII and CIII, and after 8 hours with CSII.

Time to steady state could not be determined, neither with Spearman's rank correlation (r_s), with successively exclusion of data after dose doubling or a trend index of 2 hours, respectively, nor with a Mann-Whitney U test with calculation of slope trends in intervals of 2 hours.

Clearance was used for evaluation of time to steady state. Diurnal variation of insulin clearance might partly explain why time to steady state after dose doubling not could be determined. An earlier study (T1DM patients) has found significantly higher mean insulin clearance rates with CSII in the morning (05:00–09:00 versus 23:00–03:00). The increased insulin clearance rates were most marked (>15%) in patients whose blood glucose increased during the study.[11] Another study (T1DM patients) found a significantly higher insulin clearance rate in the period 06:00–08:00 compared to 01:00–03:00.[12] This study found a highly significant correlation (r = 0.97) between the increment in insulin infusion rate and the increment in insulin clearance rate. Thus, the diurnal variation might

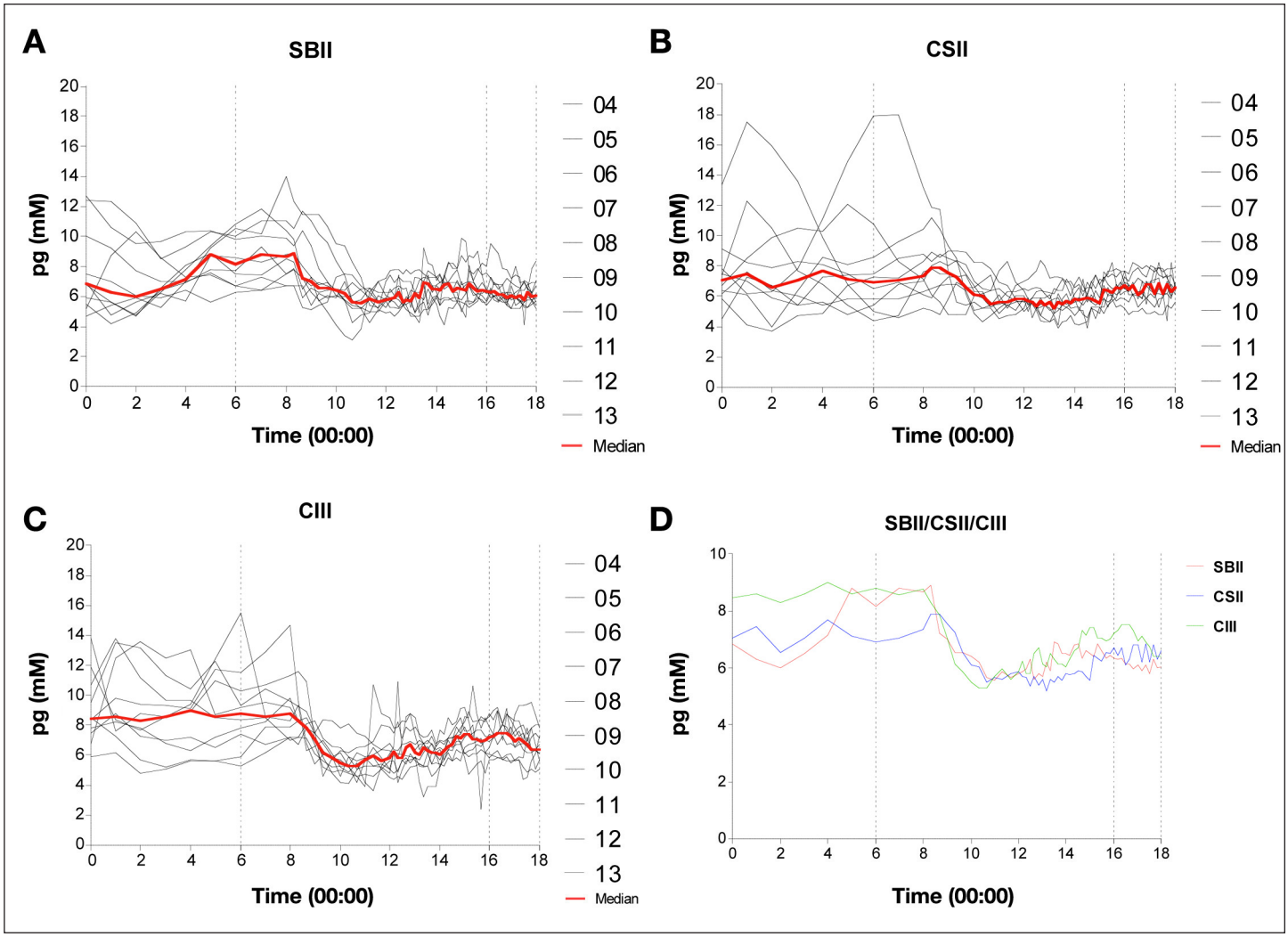

Figure 2. Individual and median serum plasma glucose (PG) with SBII, CSII, and CIII. Upper left panel: SBII, upper right panel: CSII, lower left panel: CIII, lower right panel: mean SBII, CSII, and CIII. X-axis: absolute time of the day clock. 00:00: start of fasting. 06:00: dose doubling of IAsp. 16:00–18:00: defined steady state.

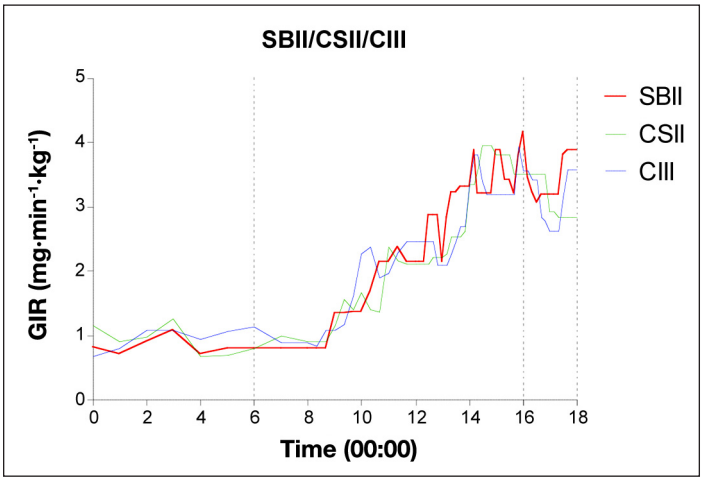

Figure 3. Median GIR: SBII, CSII, and CIII. X-axis: absolute time of the day clock. 00:00: start of fasting. 06:00: dose doubling of IAsp. 16:00–18:00: defined steady state.

also be affected by the dose doubling of IAsp at 08:00, which might further explain the difficulties of assessing time to steady state. As clearance may depend on infusion rate ($cl = R/C_{SS}$) the difference between SBII and CSII/CIII might also have an impact.

Finally, lack of power in our study probably contributes to the lack in ability to evaluate time to steady state. This topic should be systematically evaluated in studies with higher power.

As the model-based method showed extremely variable values of the variation of s-IAsp (α) and the asymptotic increase of s-IAsp (β) with SBII and CSII, the rate of increase after dose doubling could not be calculated. However, clearance estimates similar to those obtained with the nonmodel approach were obtained.

In a clinical setting, the time to achievement of a new steady state after change of dose with CSII (with the current generation of fast-acting insulins) might not be critical as the basal rate is often changed several times on a 24-hour basis in a specific pattern and with additional mealtime bolus administration.

An earlier study with insulin lispro found that steady state was achieved after 120 min with infusion rates of 0.5 and 1.0 IU/h, whereas no steady state was achieved with an infusion rate of 2.0 IU/h in the 4-hour clamp period.[7]

Our infusion rate was 1.6 ± 0.6 IU/h (mean ± SD), with a dose range of 0.8–2.5 IU/h (SBII/CSII/CIII). Thus, our infusion rate is most closely comparable with the infusion rate of 2.0 IU/h. Insulin lispro and insulin aspart are both rapid-acting insulin analogs, and thus comparable time-action profiles are expected. We found a time gap between dose doubling of IAsp with CSII and achievement of a steady-state level of approximately 8 hours.

A study with human insulin has found a time to steady state of 60–90 min with CIII and 6–8 hours with CSII (2.4 IU/h).[8] The time to steady state with CSII is in accordance with our findings, but their time to steady state with CIII is much shorter.

Based upon our results and literature evaluation, time to steady state with CSII is complex and uncertain. Two earlier studies have evaluated time to steady state with CSII (insulin lispro[7] and HI[8]). Neither of these studies state the method applied for evaluation of time to steady state.

In evaluation of the clearance results, it must be kept in mind that the model used for clearance calculation $[X(t) = \alpha + \beta(1 - \exp(-\gamma t)]$ is an approximation. Absorption of IAsp with SBII and CSII are assumed to consist of a relatively slow phase for dimers and a faster phase for monomers. Hourly bolus injections might also result in variable IAsp disappearance from the SC depot. With CSII, the model is an approximation until steady state of s-IAsp is achieved.

No significant differences in clearance between the three administration protocols were found. However, a higher number of measurements in the first hours after dose doubling (every 20 min) might have improved the pharmacokinetic analysis. A shorter sampling interval might also have made our study more informative. Furthermore, episodes of increasing and decreasing values of s-IAsp were observed in periods with expected steady state. However, we consider the obtained values for IAsp clearance to be plausible and homogeneous and in agreement with a study in healthy males where clearance of IAsp was found to be 20.33 ± 5.33 $ml \cdot min^{-1} \cdot kg^{-1}$.[6]

The finding of no significant differences in clearance between the three administration protocols is an indication of no significant SC insulin degradation, and thus equivalent bioequivalence between SC and IV administration. This issue has been a subject of considerable debate. The problem is partly related to the inconsistency concerning some of the methods used, and because of different conclusions drawn from studies in animals, in nondiabetic subjects, and in different categories of insulin-dependent patients. Another problem has been different types of insulin and insulin assays used. Identical bioavailability of SC injection of IAsp relative to that of human insulin has been reported in healthy volunteers[3] and in T1DM patients.[13]

The finding of nonsignificant differences in pharmacodynamics (effect over different time intervals) between the three administration protocols is in agreement with nonsignificant differences in pharmacokinetics. Thus, this is an indication of no clinically relevant differences between the three administration protocols. The clinical relevance of our study is evaluated on the basis of the secondary parameters PG and GIR.

Considering the time interval between dose doubling and achievement of steady state, our results indicate insignificant clinical relevance of frequent changes in SC basal insulin infusion rates on a 24-hour basis.

Conclusion

Our results indicate insignificant clinical relevance of frequent changes in SC basal insulin infusion rates on a 24-hour basis.

Regarding technological features of SC insulin pumps, no discernable advantages of increasing pump stroke frequency were found. This indicates that sophisticated changes in pump stroke frequency might not be of clinical relevance in future pumps used for basal SC insulin infusion.

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