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ORIGINAL ARTICLE

Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart

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Aims: To evaluate the pharmacokinetics and pharmacodynamics of faster-acting insulin aspart and insulin aspart in a randomized, single-centre, double-blind study.

Methods: Fifty-two patients with type 1 diabetes (mean age 40.3 years) received faster-acting insulin aspart, insulin aspart, or another faster aspart formulation (not selected for further development), each as a single 0.2 U/kg subcutaneous dose, under glucose-clamp conditions, in a three-way crossover design (3–12 days washout between dosing).

Results: Faster-acting insulin aspart had a faster onset of exposure compared with insulin aspart, shown by a 57% earlier onset of appearance [4.9 vs 11.2 min; ratio 0.43, 95% confidence interval (CI) 0.36; 0.51], a 35% earlier time to reach 50% maximum concentration (20.7 vs 31.6 min; ratio 0.65, 95% CI 0.59; 0.72) and a greater early exposure within 90 min after dosing. The greatest difference occurred during the first 15 min, when area under the serum insulin aspart curve was 4.5-fold greater with faster-acting insulin aspart than with insulin aspart. Both treatments had a similar time to maximum concentration, total exposure and maximum concentration. Faster-acting insulin aspart had a significantly greater glucose-lowering effect within 90 min after dosing [largest difference: area under the curve for the glucose infusion rate ($AUC_{GIR,0-30\,min}$ ratio 1.48, 95% CI 1.13; 2.02] and 17% earlier time to reach 50% maximum glucose infusion rate (38.3 vs 46.1 min; ratio 0.83, 95% CI 0.73; 0.94). The primary endpoint ($AUC_{GIR,0-2\,h}$) was 10% greater for faster-acting insulin aspart, but did not reach statistical significance (ratio 1.10, 95% CI 1.00; 1.22). Both treatments had similar total and maximum glucose-lowering effects, indicating similar overall potency.

Conclusions: Faster-acting insulin aspart was found to have earlier onset and higher early exposure than insulin aspart, and a greater early glucose-lowering effect, with similar potency.

Keywords: faster-acting insulin aspart, pharmacodynamics, pharmacokinetics, postprandial glucose, type 1 diabetes

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Introduction

Elevated postprandial glucose levels are an important contributor to overall hyperglycaemia in diabetes, and control of postprandial hyperglycaemia is an important factor for achieving glycated haemoglobin (HbA1c) targets [1,2]. In individuals without diabetes, the physiological insulin response to a glucose load begins with a transient first-phase insulin secretion [3] that is deficient in type 2 diabetes [4,5]. The role of first-phase insulin secretion in controlling postprandial glucose appears to be largely mediated at the level of the liver, by enabling prompt suppression of endogenous glucose production [5,6]. Early administration of insulin to help restore first-phase insulin secretion is associated with improved postprandial glucose tolerance [4,5]. The challenge is the delayed absorption of insulin into the blood, after its injection into subcutaneous (s.c.) tissue, leading to insulin response profiles that differ from normal physiological insulin secretion [7].

Rapid-acting insulin analogues were developed to more closely approach the physiological insulin response, compared with regular human insulin, and represented a step forward in postprandial glucose control [8–10]. Nevertheless, despite improvements in pharmacokinetic (PK) and pharmacodynamic (PD) profiles, current rapid-acting insulin analogues are still absorbed too slowly and do not replicate the physiological insulin secretion profile in healthy individuals [7,11,12]. Consequently, an injection–meal interval may be required to achieve optimum postprandial glucose control [11–13], which requires extra vigilance by patients. Moreover, recent findings from an observational study of hospital-based cardiology units within a community healthcare system have highlighted the need for improved coordination of mealtime insulin practices in several areas, including timing of blood glucose testing and rapid-acting insulin administration [14]. Results showed that only 14% (n = 64) of patients received blood glucose testing <1 h before administration of insulin and insulin administration within 15 min of the meal. Furthermore, results

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from a study evaluating how patients with type 1 diabetes receiving regular human insulin respond to diabetologists' recommendations relating to intensified insulin therapy showed that, despite suggestions for an injection–meal interval of 30 min, most patients use a short (<15 min) injection–meal interval in daily life [15].

Faster-acting insulin aspart is insulin aspart set in a new formulation containing two well-known excipients, nicotinamide and arginine. The excipients result in a stable formulation and faster initial absorption after s.c. injection, and are predicted to create a more physiological insulin profile with a resultant improvement in postprandial glycaemic excursions. Both excipients are included in the US Food and Drug Administration (FDA) list of inactive ingredients for approved drug products for injection [16].

The aim of the present study was to evaluate the PK and PD properties of faster-acting insulin aspart, compared with the currently marketed formulation of this rapid-acting analogue, insulin aspart (NovoRapid®/NovoLog®), in a euglycaemic clamp setting, with particular focus on the early time period after dosing.

Materials and Methods

Study Design

This was a randomized, double-blind, single-dose, single-centre, three-period, complete crossover, phase I trial in subjects with type 1 diabetes. The trial protocol was reviewed and approved by the local health authority (Bundesinstitut für Arzneimittel und Medizinprodukte) in accordance with regulations, and by the appropriate independent ethics committee (Ärztekammer Nordrhein). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice, as defined by the International Conference on Harmonisation. Written informed consent was obtained before any trial-related activity was initiated. The trial (NN1218-3978) is registered at ClinicalTrials.gov (ID number: NCT01618188).

Subjects

Study participants were enrolled at Profil, Neuss, Germany. Eligible subjects were men and women aged 18–64 years (both inclusive), diagnosed with type 1 diabetes for a minimum of 12 months before inclusion in the trial, treated with multiple daily insulin injections or continuous s.c. insulin infusion for ≥12 months (total daily insulin dose <1.2 IU/kg/day and total daily bolus insulin dose <0.7 IU/kg/day), with an HbA1c concentration ≤8.5%, a body mass index of 18–28 kg/m^2 and fasting C-peptide concentration ≤0.3 nmol/l.

Individuals with clinically significant concomitant diseases, history of recurrent severe hypoglycaemia or hypoglycaemic unawareness, or those who were pregnant or breastfeeding were excluded.

Interventions

The trial comprised a screening visit (visit 1), three dosing visits (visits 2–4; separated by washout periods of 3–12 days, during which normal insulin treatment was resumed), and a follow-up visit (visit 5). Screening took place 2–21 days before visit 2 and the follow-up visit took place 2–21 days after the last dosing visit. At dosing visits, subjects received a single dose of 0.2 U/kg faster-acting insulin aspart, insulin aspart or a different formulation of faster-acting insulin aspart that is no longer being investigated in clinical studies and, hence, data for this formulation are not reported in the present study (all Novo Nordisk, Bagsvaerd, Denmark); the sequence of treatment was randomly assigned.

Study medications were provided in 3 ml Penfill® cartridges (100 U/ml; Novo Nordisk) and were administered by s.c. injection with a syringe and needle into a lifted skinfold of the lower abdominal wall above the inguinal area by a person otherwise not involved in the study, to maintain the double-blind character of the study.

The present article reports data on the faster-acting insulin aspart formulation that is being pursued in current and future clinical development.

Clamp Procedure

At each dosing visit, subjects attended the trial site at 07:00 hours having fasted since 22:00 hours the previous evening, with the exception of water and ≤20 g of rapidly absorbable carbohydrate to prevent short-term hypoglycaemia. If hypoglycaemia occurred <24 h before dosing, the dosing visit was rescheduled or the subjects were withdrawn from the trial. At the dosing visit, subjects underwent a 12-h euglycaemic clamp procedure performed using a Biostator® device (MTB Medizintechnik, Amstetten, Germany), as described previously [17,18]. In brief, 1–6 h before dosing of the trial product, subjects received a variable intravenous infusion of human insulin (15 IU Actrapid®, Novo Nordisk: 100 IU/ml in 49 ml saline and 1 ml of the subject's blood) or glucose (20%) to obtain a blood glucose clamp target level of 5.5 mmol/l (100 mg/dl). The trial product was administered after subjects' blood glucose had been stable for at least 1 h without any glucose infusion. After trial product administration, the rate of insulin infusion (if any) was reduced gradually and stopped completely when blood glucose had decreased by 0.3 mmol/l (5 mg/dl); glucose infusion was then initiated to maintain the glucose concentration constant at the glucose clamp target of 5.5 mmol/l (100 mg/dl). The clamp continued for 12 h post-dosing of trial product, but was terminated earlier if blood glucose consistently exceeded 11.1 mmol/l (200 mg/dl) without any glucose having been administered for at least 30 min.

Blood glucose was measured continuously by the Biostator, and the glucose infusion rate (GIR) required to maintain the blood glucose concentration at the target level was recorded every minute throughout the euglycaemic clamp. Blood glucose measurements from the Biostator were checked regularly against those obtained by means of a glucose analyser (Super GL Glucose Analyser). During the entire clamp procedure, subjects remained fasting (no oral intake other than water) and stayed in a supine or semi-supine position.

Assessments

Pharmacokinetics. Secondary PK endpoints included the following: area under the curve (AUC) for various time intervals: $AUC_{0-15\,min}$, $AUC_{0-30\,min}$, $AUC_{0-1\,h}$, $AUC_{0-1.5\,h}$ (*post hoc* endpoint), $AUC_{0-2\,h}$ and $AUC_{0-12\,h}$ (i.e. total exposure), maximum concentration (C_{max}), time to maximum concentration (t_{max}), time to reach 50% maximum concentration ($t50\%C_{max}$; *post hoc* endpoint) and onset of appearance [defined as time from study drug administration until the first time free serum insulin aspart concentrations were equal to or higher than the lower limit of quantification (20 pmol/l)].

Pharmacokinetic samples were taken at the following times: before dosing (<5 min before trial product administration), then at 2-min intervals until 20 min after dosing, at 5-min intervals from 20 to 80 min after dosing, at 10-min intervals from 80 min to 2 h after dosing, at 15-min intervals from 2 to 3 h after dosing, at 30-min intervals from 3 to 4 h after dosing, at 1-h intervals from 4 to 8 h after dosing and at 2-h intervals from 8 to 12 h after dosing. Free serum insulin aspart concentrations were quantified using a validated insulin aspart-specific enzyme-linked immunosorbent assay.

Pharmacodynamics. The primary study endpoint was the AUC for the GIR from 0 to 2 h ($AUC_{GIR,\,0-2\,h}$). Secondary PD endpoints included $AUC_{GIR,\,0-30\,min}$, $AUC_{GIR,\,0-1\,h}$, $AUC_{GIR,\,0-1.5\,h}$, $AUC_{GIR,\,0-12\,h}$ (i.e. total glucose-lowering effect), maximum GIR (GIR_{max}), time to maximum GIR ($tGIR_{max}$) and time to reach 50% maximum GIR ($t50\%GIR_{max}$; *post hoc* endpoint).

Safety. Safety endpoints included treatment-emergent adverse events (TEAEs) and hypoglycaemic episodes, local tolerability at injection site, and changes in physical examination and vital signs. A TEAE was defined as an adverse event that, for each treatment period, occurred after administration of the study product, but no later than 7 days after the administration.

Hypoglycaemia was defined as any episode of severe hypoglycaemia, as per the American Diabetes Association definition (hypoglycaemia requiring third-party assistance) [19] or minor hypoglycaemia: a minor hypoglycaemic episode was defined as either an episode with symptoms consistent with hypoglycaemia, verified by a plasma glucose concentration <3.1 mmol/l (56 mg/dl), and the patient being able to manage him/herself, or an asymptomatic plasma glucose concentration <3.1 mmol/l (56 mg/dl). A hypoglycaemic episode was considered as treatment-emergent if, for each treatment period, the onset occurred after administration of study product, but no later than 1 day after the administration.

Statistical Methods

It was calculated that with 48 subjects completing the trial, a ratio of 1.21 for faster-acting insulin aspart versus insulin aspart for the primary endpoint, $AUC_{GIR,\,0-2\,h}$, could be detected with 80% power using a two-sided test and a 5% level of significance and assuming a residual standard deviation of 0.32. Accordingly, to allow for drop-outs, a total of 52 subjects were planned to be randomized.

Analyses of the PK and PD endpoints were based on the full analysis set, comprising all randomized subjects who received at least one dose of faster-acting insulin aspart, insulin aspart, or the other formulation of faster-acting insulin aspart.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). For PK and PD analyses, a significance level of 5% was used.

Analyses of the safety endpoints were based on the safety analysis set, comprising all subjects who received at least one dose of faster-acting insulin aspart, insulin aspart or the other formulation of faster-acting insulin aspart. Safety endpoints were summarized using descriptive statistics.

Pharmacokinetics. The AUC endpoints and C_{max} were analysed using a linear mixed model for the log-transformed endpoint, with treatment and period as fixed effects and subject as a random effect. The same model without log-transformation was used to analyse onset of appearance, $t50\%C_{max}$ and t_{max}; Fieller treatment ratio and 95% confidence intervals (CIs) were calculated for these endpoints (*post hoc* analysis). The serum insulin aspart concentration–time curves were fitted using compartmental modelling and the fitted curves were used for calculation of onset of appearance and for calculation of AUC in the time interval from time of trial product administration (time 0) to time of first PK sample above the lower limit of quantification. After this time, AUCs were calculated using the linear trapezoidal method on observed data and actual profile time (i.e. time since trial product administration). Interpolated values at the end of the interval were used for calculation of partial AUCs.

Pharmacodynamics. The primary endpoint $AUC_{GIR,\,0-2\,h}$ and the secondary PD endpoints $AUC_{GIR,\,0-1\,h}$, $AUC_{GIR,\,0-1.5\,h}$, $AUC_{GIR,\,0-12\,h}$ and GIR_{max} were analysed using a linear mixed model for the log-transformed endpoint, with treatment and period as fixed effects and subject as a random effect. The same model without log-transformation was used to analyse $AUC_{GIR,\,0-30\,min}$ (as the planned log-transformation was not feasible because some AUCs were equal to 0), $tGIR_{max}$ and $t50\%GIR_{max}$; Fieller treatment ratio and 95% CI were calculated for $AUC_{GIR,\,0-30\,min}$, $tGIR_{max}$ (*post hoc* analysis) and $t50\%GIR_{max}$ (*post hoc* analysis). Smoothed GIR profiles were used for calculation of GIR_{max}, $tGIR_{max}$ and $t50\%GIR_{max}$.

Table 1. Baseline characteristics.

Characteristic	Total (N = 52)
Age*, years	40.3 (12.0)
Gender	
Female, n (%)	9 (17.3)
Male, n (%)	43 (82.7)
Body weight*, kg	76.9 (10.2)
Body mass index*, kg/m^2	24.2 (2.2)
Duration of diabetes*, years	20.2 (11.4)
HbA1c*, %	7.3 (0.7)
Fasting C-peptide <0.3 nmol/l, n	52†

HbA1c, glycated haemoglobin.
*Mean (standard deviation).
†Forty out of 52 subjects had fasting C-peptide values below the lower limit of quantification (0.02 nmol/l).

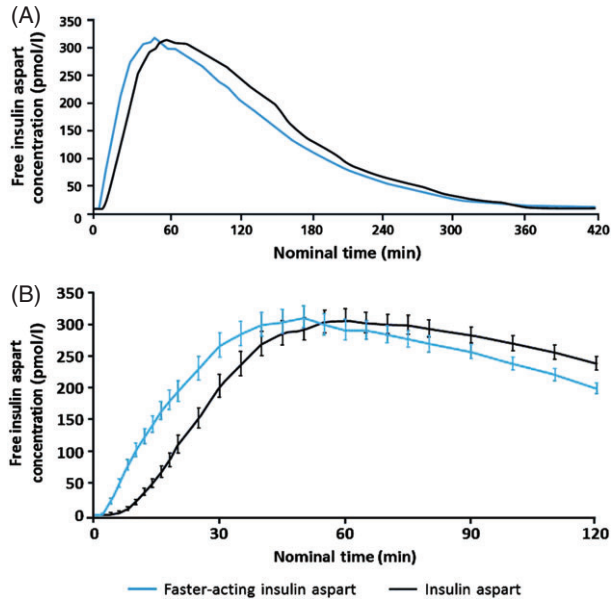

Figure 1. Mean (± standard error of the mean) concentration–time profiles for faster-acting insulin aspart and insulin aspart from (A) 0–7 h and (B) 0–2 h (early phase).

Smoothing was done by means of the LOESS method (smoothing parameter 0.10). AUCs for GIR were calculated using the step function method.

Results

Demographic and Baseline Characteristics of Subjects

Baseline characteristics of study participants are provided in Table 1. Of 73 subjects screened, a total of 52 white subjects (43 men, 9 women; mean age 40 years) were randomized and exposed to study drugs, and 51 completed the trial. One subject was withdrawn (at his own request) after one dosing visit, during which he received the other formulation of faster-acting insulin aspart.

Pharmacokinetics

Insulin Concentration Profiles. The mean concentration–time profiles for serum insulin aspart after administration of faster-acting insulin aspart were shifted to the left, compared with those after administration of insulin aspart, indicating a faster onset and greater early insulin exposure with faster-acting insulin aspart (Figure 1A, B).

Onset of Insulin Exposure. A faster initial onset of absorption of faster-acting insulin aspart versus insulin aspart was supported by a significantly earlier onset of appearance (4.9 vs 11.2 min) and t50%C_{max} (20.7 vs 31.6 min; Table 2). With faster-acting insulin aspart, the time to onset of appearance and t50%C_{max} were reduced by 57 and 35%, respectively, compared with insulin aspart. The t_{max} for faster-acting insulin aspart was 62.9 min and for insulin aspart it was 69.7 min; thus, t_{max} was 10% faster for faster-acting insulin aspart than for insulin aspart, but this difference between the two treatments did not reach statistical significance (ratio 0.90, 95% CI 0.79; 1.03).

Early Insulin Exposure. The exposure for each of the early partial AUCs for serum insulin aspart covering the first 90 min after dosing ($AUC_{0–15\,min}$, $AUC_{0–30\,min}$, $AUC_{0–1\,h}$ and $AUC_{0–1.5\,h}$) were all significantly larger for faster-acting insulin aspart than for insulin aspart (Table 2).

The largest difference occurred during the first 15 min when the area under the serum insulin aspart curve with faster-acting insulin aspart was four and a half times greater than that observed with insulin aspart (treatment ratio 4.53, 95% CI 3.62; 5.66).

Table 2. Pharmacokinetic results, based on free serum insulin aspart, for faster-acting insulin aspart and insulin aspart.

	Faster-acting insulin aspart (N = 51) LS mean (CV or s.e.m.*)	Insulin aspart (N = 51) LS mean (CV or s.e.m.*)	Treatment ratio (95% CI) faster-acting insulin aspart/insulin aspart
Onset of insulin exposure, min			
Onset of appearance	4.9 (0.45)*	11.2 (0.45)*	0.43 (0.36; 0.51)
t50%C_{max}	20.7 (1.03)*	31.6 (1.03)*	0.65 (0.59; 0.72)
t_{max}	62.9 (3.73)*	69.7 (3.73)*	0.90 (0.79; 1.03)
Early insulin exposure, pmol × h/l			
$AUC_{0–15\,min}$	14.0 (0.12)	3.1 (0.12)	4.53 (3.62; 5.66)
$AUC_{0–30\,min}$	59.9 (0.09)	29.2 (0.09)	2.05 (1.76; 2.38)
$AUC_{0–1\,h}$	196.5 (0.07)	153.4 (0.07)	1.28 (1.15; 1.43)
$AUC_{0–1.5\,h}$	328.8 (0.06)	295.4 (0.06)	1.11 (1.01; 1.22)
$AUC_{0–2\,h}$	441.9 (0.06)	424.5 (0.06)	1.04 (0.95; 1.14)
Overall exposure			
$AUC_{0–12\,h}$, pmol × h/l	755.7 (0.05)	786.9 (0.05)	0.96 (0.87; 1.06)
C_{max}, pmol/l	318.5 (0.06)	324.4 (0.06)	0.98 (0.90; 1.07)

LS means with CVs (calculated as the standard error of the log-transformed endpoints) or *s.e.m. values, and treatment comparisons with two-sided 95% CIs are presented. Fieller treatment ratio and 95% CIs were calculated for onset of appearance, t50%C_{max} and t_{max}.

AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; LS, least squares; s.e.m., standard error of the mean; t_{max}, time to maximum concentration; t50%C_{max}, time to reach 50% maximum concentration.

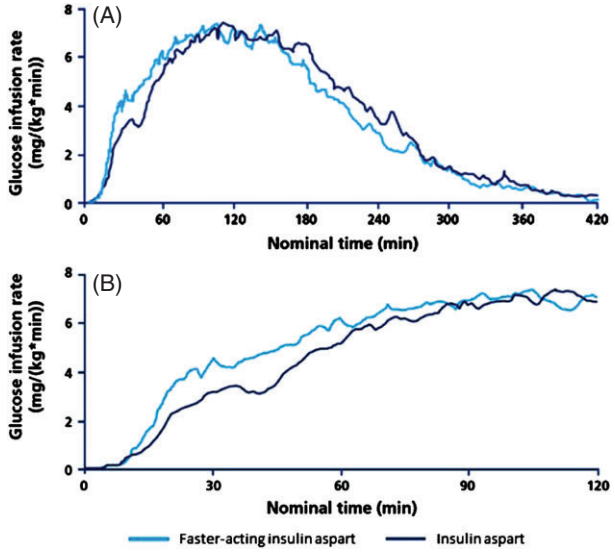

Figure 2. Glucose-lowering effect (raw mean glucose infusion rate profiles) of faster-acting insulin aspart and insulin aspart from (A) 0–7 h and (B) 0–2 h (early phase).

Total Insulin Exposure. Total exposure ($AUC_{0-12\,h}$) and C_{max} were similar for faster-acting insulin aspart and insulin aspart (Table 2).

Pharmacodynamics

Glucose Infusion Profiles. The raw mean GIR profiles after administration of faster-acting insulin aspart were shifted to the left, compared with those after administration of insulin aspart, indicating a faster onset and greater early glucose-lowering effect with faster-acting insulin aspart (Figure 2A, B).

Onset of Glucose-lowering Effect. The faster initial onset of absorption and higher early exposure translated into a faster onset of the glucose-lowering effect of faster-acting insulin aspart compared with insulin aspart, supported by a significantly earlier $t50\%GIR_{max}$ (38.3 vs 46.1 min) and a non-significant trend towards earlier $tGIR_{max}$ (124.3 vs 135.2 min; Table 3). With faster-acting insulin aspart, the $t50\%GIR_{max}$ and $tGIR_{max}$ were reduced by 17 and 8%, respectively, compared with insulin aspart.

Early Glucose-lowering Effect. Faster-acting insulin aspart had a significantly earlier and higher glucose-lowering effect (indicated by a greater AUC_{GIR}) in the first 1.5 h after injection, compared with insulin aspart (Table 3). At 2 h after injection (primary endpoint: $AUC_{GIR,\,0-2\,h}$), the difference between the two treatments was 10% larger for faster-acting insulin aspart than for insulin aspart, but did not reach statistical significance (ratio 1.10, 95% CI 1.00; 1.22).

The largest difference occurred during the first 30 min when the area under the GIR curve with faster-acting insulin aspart was one and a half times greater than that observed with insulin aspart (treatment ratio 1.48, 95% CI 1.13; 2.02).

Total Glucose-lowering Effect. The total glucose-lowering effect ($AUC_{GIR,\,0-12\,h}$) and GIR_{max} were similar for faster-acting insulin aspart and insulin aspart (Table 3).

Safety

Both faster-acting insulin aspart and insulin aspart were well tolerated and no unexpected safety issues were reported during the study. Overall, the percentage of subjects reporting at least one TEAE was low for both faster-acting insulin aspart and insulin aspart (9.8 and 7.8%, respectively). Headache was the most common TEAE, occurring in 5.9% of subjects with both faster-acting insulin aspart and insulin aspart. All TEAEs were mild in severity, and no serious adverse events or injection site reactions were observed after treatment administration. Two treatment-emergent hypoglycaemic episodes were observed,

Table 3. Pharmacodynamic results for faster-acting insulin aspart and insulin aspart.

	Faster-acting insulin aspart (N = 51) LS mean (CV or s.e.m.*)	Insulin aspart (N = 51) LS mean (CV or s.e.m.*)	Treatment ratio (95% CI) faster-acting insulin aspart/insulin aspart
Onset of glucose-lowering effect, min			
$t50\%GIR_{max}$	38.3 (2.22)*	46.1 (2.22)*	0.83 (0.73; 0.94)
$tGIR_{max}$	124.3 (5.87)*	135.2 (5.87)*	0.92 (0.84; 1.01)
Early glucose-lowering effect, mg/kg			
$AUC_{GIR,\,0-30\,min}$	56.2 (4.88)*	38.0 (4.88)*	1.48 (1.13; 2.02)
$AUC_{GIR,\,0-1\,h}$	183.7 (0.07)	140.2 (0.07)	1.31 (1.18; 1.46)
$AUC_{GIR,\,0-1.5\,h}$	360.4 (0.07)	308.3 (0.07)	1.17 (1.05; 1.30)
$AUC_{GIR,\,0-2\,h}$	554.5 (0.07)	502.2 (0.07)	1.10 (1.00; 1.22)
Overall glucose-lowering effect			
$AUC_{GIR,\,0-12\,h}$, mg/kg	1375.2 (0.06)	1404.7 (0.06)	0.98 (0.87; 1.11)
GIR_{max}, mg/(kg × min)	7.2 (0.05)	7.1 (0.05)	1.02 (0.93; 1.12)

LS means with CVs (calculated as the standard error of the log-transformed endpoints) or *s.e.m. values, and treatment comparisons with two-sided 95% CIs are presented. Fieller treatment ratio and 95% CIs were calculated for $t50\%GIR_{max}$, $tGIR_{max}$ and $AUC_{GIR,\,0-30\,min}$.

AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; GIR, glucose infusion rate; GIR_{max}, maximum glucose infusion rate; LS, least squares; s.e.m., standard error of the mean; $tGIR_{max}$, time to maximum glucose infusion rate; $t50\%GIR_{max}$, time to reach 50% maximum glucose infusion rate.

one each in the faster-acting insulin aspart and insulin aspart treatment groups. One episode occurred >17 h after administration of the study medication (faster-acting insulin aspart), at a time when the subject had already begun using their own insulin (last injection ~4 h before the hypoglycaemic episode). The other episode occurred 12 h after administration of the study medication (insulin aspart) under clamp conditions, but this clamp had been terminated early because of high blood glucose concentrations and the subject had injected human soluble insulin ~5 h before the hypoglycaemic episode; therefore, both episodes were judged to be unrelated to study medication.

Discussion

The results of the present study show that faster-acting insulin aspart had a faster onset of appearance and higher early exposure, which resulted in a greater early glucose-lowering effect in subjects with type 1 diabetes, compared with insulin aspart. Based on GIR in the first 30 min after dosing ($AUC_{GIR,0-30\,min}$), the difference in early glucose-lowering effect between faster-acting insulin aspart and insulin aspart (treatment ratio 1.48, 95% CI 1.13; 2.02; Figure 3A) in the present study is similar to that between insulin aspart and regular human insulin (ratio 1.38, 95% CI 0.78; 2.89; Figure 3B; data on file and adapted from Heinemann et al. [20]); both datasets were analysed in the same manner. The clinical benefits of having a faster onset and greater early exposure with faster-acting insulin aspart will need to be demonstrated in large clinical studies.

An ultra-rapid-acting insulin with an increased rate of absorption to more closely approach the physiological insulin secretion profile – particularly the early rise in plasma insulin concentration – could lead to improved postprandial glucose control and earlier inhibition of hepatic glucose production [5,7,21]. An ultra-rapid-acting insulin could also provide more flexibility for patients in terms of dosing, both pre- and post-meal, compared with currently available rapid-acting analogues and regular human insulin [22]. Accordingly, faster-acting insulin aspart has the potential to build on the benefits of currently available rapid-acting insulin analogues that have been shown to control postprandial glucose excursions better than regular human insulin [10]. There is interest in developing ultra-rapid-acting insulins that may hold promise for advancing diabetes treatment, including the performance of both s.c. insulin injection and closed-loop applications [23,24]. Several other potential approaches are being investigated [7,25,26], which emphasizes the extent of the current unmet need.

The safety and tolerability profile of faster-acting insulin aspart is expected to be similar to that of insulin aspart, which has a long-established favourable safety profile, based on substantive clinical experience with NovoRapid®/NovoLog® that launched more than 10 years ago. In the present study, faster-acting insulin aspart was well tolerated and no safety concerns were raised. The excipients, nicotinamide and arginine, are unlikely to have an impact on the safety and tolerability profile of faster-acting insulin aspart, and are included in the FDA list of inactive ingredients for approved drug products for injection [16].

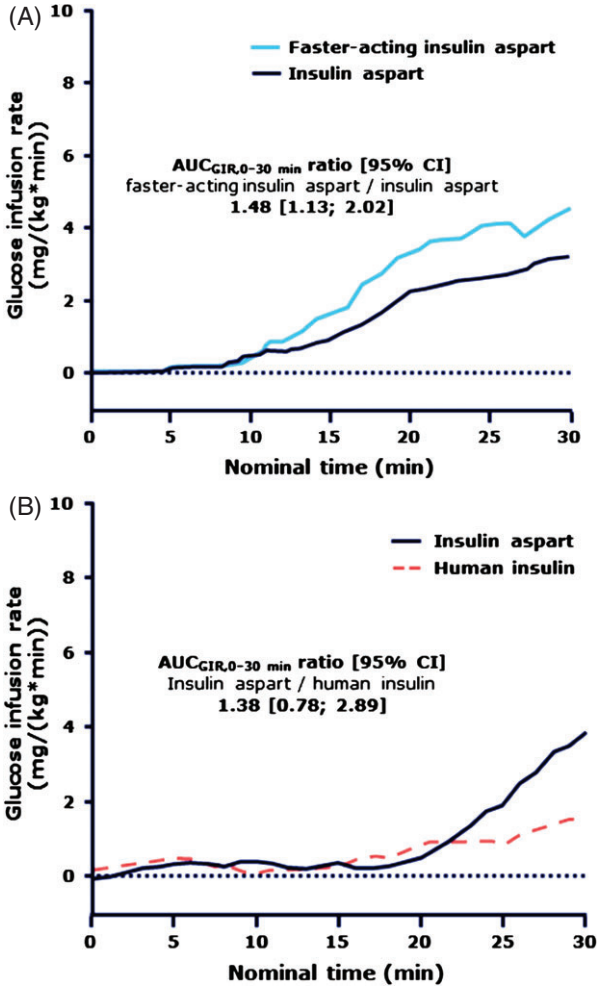

Figure 3. Early glucose-lowering effect [mean glucose infusion rate (GIR) profiles] of (A) faster-acting insulin aspart and insulin aspart and (B) insulin aspart and human insulin (data on file and adapted from Heinemann et al. 1997 [20]). The GIR endpoint [area under the curve $(AUC)_{GIR,0-30\,min}$] for both studies was analysed using a linear mixed-model with treatment and period as fixed effects, and subject as a random effect. Ratios and corresponding confidence intervals (CIs) were estimated using Fieller's method.

The strengths of the present study include its complete crossover design that enables the subjects to act as their own control, and the enrolment of subjects with type 1 diabetes that enables investigation of clinically relevant PD outcomes at therapeutic doses without introducing a confounding factor of endogenous insulin production. A limitation of the study is the experimental glucose clamp setting, which makes it difficult to translate the findings into the 'real-life' practice situation and, therefore, evaluate the clinical relevance of the observed PK/PD differences between faster-acting insulin aspart and insulin aspart. Nevertheless, the clinical relevance of these differences is illustrated by findings from a meal challenge study in 36 subjects with type 1 diabetes. The faster onset of exposure of another formulation of faster-acting insulin aspart [FIA(B)], with a PK profile close to that seen in the present study, was associated with a greater early postprandial

glucose-lowering effect, indicated by a 26% lower post-meal $\Delta AUC_{blood\ glucose,\ 0-2\,h}$, and 33% improvement in total postprandial glycaemic control (based on $\Delta AUC_{blood\ glucose,\ 0-6\,h}$), compared with insulin aspart [27].

In conclusion, the results of the present study, in conjunction with those from the meal challenge study [27], indicate that faster-acting insulin aspart had twice as fast an onset of appearance and a twofold higher insulin concentration, in addition to a 50% greater glucose-lowering effect within the first 30 min, in subjects with type 1 diabetes, compared with the currently available rapid-acting insulin analogue insulin aspart. More closely approaching the physiological insulin secretion profile could translate into additional clinical benefits, such as earlier inhibition of hepatic glucose production and improved postprandial glucose control [5,7,21]. The efficacy and safety of faster-acting insulin aspart will require further investigation in subjects with diabetes in large clinical studies.

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Conflict of Interest

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