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Insulin glulisine: a faster onset of action compared with insulin lispro

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Aim: This randomized, single-centre, double-blind, crossover study compared the pharmacodynamic and pharmacokinetic properties of two different doses of insulin glulisine (glulisine) and insulin lispro (lispro) in lean to obese subjects.

Methods: Eighty subjects without diabetes, stratified into four body mass index (BMI) classes (<25, ≥ 25 to <30, ≥ 30 to <35 and ≥ 35 kg/m^2), were randomized to receive single injections of glulisine and lispro (0.2 and 0.4 U/kg) on four study days under glucose clamp conditions. Glucose infusion rates (GIR) and insulin (INS) concentrations were assessed for 10 h postdose.

Results: Glulisine showed a greater early metabolic action than lispro [GIR-area under the curve (GIR-AUC) between 0 and 1 h (0.2 U/kg: 102.3 ± 75.1 vs. 83.1 ± 72.8 mg/kg, $p < 0.05$; 0.4 U/kg: 158.0 ± 100.0 vs. 112.3 ± 70.8 mg/kg, $p < 0.001$)], with an earlier time to 10% of total GIR-AUC (0.2 U/kg: 1.4 ± 0.4 vs. 1.5 ± 0.4 h; 0.4 U/kg: 1.4 ± 0.3 vs. 1.5 ± 0.3 h, $p < 0.05$). The total metabolic effect was not different between the two insulins. In accordance with these findings, the time to 10% of total INS-AUC was faster with glulisine compared with lispro at either dose (0.2 U/kg: 0.7 ± 0.2 vs. 0.8 ± 0.2 h; 0.4 U/kg: 0.8 ± 0.2 vs. 0.9 ± 0.2 h, $p < 0.001$). The faster rise in insulin concentrations and the earlier onset of activity of glulisine vs. lispro was consistently observed in each individual BMI class.

Conclusions: Glulisine shows a faster onset of action than lispro, independent of BMI and dose.

Keywords: glucose clamp, insulin analogues, pharmacodynamics, pharmacokinetics
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Introduction

The therapeutic concept of 'intensified insulin therapy' aims at substituting the complex pattern of endogenous insulin secretion in people with diabetes. The aim of subcutaneous (s.c.) injections of short-acting insulin before meals is to mirror prandial insulin secretion, while the aim of retarded insulin preparations is to substitute basal insulin secretion [1,2]. Unfortunately, the time–action profile of s.c. injected regular human insulin (RHI) shows a slow onset of action (with a peak metabolic effect approximately 3 h postdosing [3]) and a prolonged duration of action beyond 8 h [4], which impedes the attainment of good postprandial blood glucose (BG) control without suffering from late postprandial hypoglycaemia [5]. Consequently, insulin products comprising of human insulin analogues with a faster onset of action and a shorter duration of action than RHI were developed and are now widely used. These insulins, used in intensified basal-bolus insulin

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regimens, enable achievement of tighter postprandial BG control, potentially resulting in improved metabolic control [6].

Insulin glulisine (glulisine) is a new, fast-acting recombinant human insulin analogue. It differs from RHI by the replacement of asparagine at position B3 by lysine, and lysine at position B29 by glutamic acid (Lys[B3], Glu[B29] human insulin). Glulisine, like other rapid-acting insulin analogues, displays a more rapid onset of action and a shorter duration of action vs. RHI [7], leading to improved postprandial BG concentrations [8] and better overall diabetes control [9].

Time–action profiles of currently available s.c. insulin products are prolonged with higher doses, and attenuated and delayed in obese subjects [10,11], which is unwanted. This phenomenon is most pronounced with RHI, which has a substantially longer duration of action with higher doses [4] and is particularly evident in subjects with a high body weight. These subjects not only have to inject higher insulin doses to obtain the same amount of insulin units per kilogram body weight, but also have to compensate for the insulin resistance associated with obesity. Fast-acting insulin analogues such as insulin aspart (aspart) and insulin lispro (lispro) also last longer when injected at higher doses [4,12], although for substantially less time compared with RHI. In a recent manual euglycaemic clamp study, glulisine was shown to have shorter times to onset of activity compared with lispro in non-diabetic, obese [body mass index (BMI) 30–40 kg/m^2] subjects [13]. Indeed, in that study, lispro displayed a delayed action profile compared with glulisine, as indicated by smaller fractional areas under the glucose infusion rate curve (GIR-AUCs) and longer time to 20% of total glucose disposal (GIR-$t_{20\%}$) ($p = 0.025$ at 2 h). In view of the potential clinical importance of this finding, this single-centre, randomized, double-blind, four-way, crossover study was carried out to characterize the observed differences in the pharmacokinetic (PK) and pharmacodynamic (PD) properties of glulisine and lispro in a population with a wider range of BMIs. This Biostator-supported euglycaemic clamp study focussed on early exposure and action with a standard dose of 0.2 U/kg and with 0.4 U/kg as a high dose.

Methods

The study was conducted from 13 April 2004 to 21 October 2004 in accordance with the ethical principles of the Declaration of Helsinki and of Good Clinical Practice. The clinical study protocol, informed consent documents and other appropriate study-related documents were reviewed and approved by an independent ethics committee, and all subjects provided written informed consent.

The study was performed in a single centre, in male and female subjects without diabetes, aged 18–65 years, with haemoglobin A_{1c} levels in the normal range. Subjects were stratified by BMI as follows: <25 kg/m^2 (lean), ≥ 25 to <30 kg/m^2 (overweight), ≥ 30 to <35 kg/m^2 (moderately obese) and ≥ 35 kg/m^2 (severely obese). Subjects were not receiving any regular concomitant treatment with prescribed drugs on entry of the study and in the 4 weeks before screening, with the exception of oral contraceptive agents in female subjects. Subjects received either 0.2 or 0.4 U/kg of glulisine or lispro, in a randomized, double-blind order, on four separate treatment days under euglycaemic clamp conditions. The commercial products of glulisine and lispro were supplied by Aventis Pharma Deutschland GmbH (Bad Soden, Germany). A randomization schedule (generated under the directive of the Department of Biometrics and Data Management, Aventis Pharma Deutschland GmbH) linked sequential subject numbers to treatment sequence codes allocated at random.

Subjects fasted overnight prior to the day of receiving study treatment. In the morning of each of the trial days, subjects were admitted to the research institute and connected to a Biostator [glucose-controlled insulin infusion system; MTB Medizintechnik, Ulm, Germany]. After a baseline period of 90 min, the study medication was administered by s.c. injection into the periumbilical region of the abdomen using a standardized skinfold technique and a 1 ml syringe with a needle length of 12 mm. Injection sides were changed between 5 cm left and 5 cm right of the umbilicus from experiment to experiment. The study medication was administered preferably by the same physician (only in exceptional case by a substitute) at all treatment sessions.

The Biostator measured BG continuously and automatically adjusted the infusion rate of a 20% glucose solution every minute to maintain BG levels at 10% below the individual fasting BG concentrations (determined as the mean of the three BG values measured 60, 30 and 5 min before study drug administration). The Biostator also automatically initiated and calculated GIR. The glucose clamp lasted for 10 h postdosing. Venous blood samples for determination of insulin glulisine and insulin lispro concentrations in serum were collected at the following times: $-90, -60, -30, 0, 10, 20, 30, 40, 50, 60, 90, 120, 150$, 180, 210, 240, 270, 300, 360, 420, 480, 540 and 600 min. Additionally, blood samples were taken at intervals of ≤ 30 min for BG measurements with a laboratory device using the glucose-oxidase method (Super GL Ambulance

glucose analyser; Hitado Diagnostic Systems, Möhnesee, Germany) to readjust the Biostator BG measurements, if necessary. Subjects remained fasted during the entire glucose clamp period.

Venous blood samples for determination of serum C-peptide concentrations were collected at the following times: −90, 0, 60, 120, 180, 240, 300, 360, 420, 480, 540 and 600 min. A conventional radioimmunoassay (RIA) was used to measure serum C-peptide concentrations (Immulite C-Peptide; EURO/DPC, Llanberis, UK).

RIAs specific for glulisine and lispro (competitive-binding RIA; supplied by Linco Research, St Charles, MO, USA) were used to determine the concentrations in serum. Duplicate measurements were performed using a Cobra™ II series 5010 multidetector auto-gamma counting device (Packard, Meriden, CT, USA). Interbatch accuracy ranged from 94 to 112% for glulisine and from 93 to 108% for lispro. The interbatch precisions were 3.1–8.8 CV% (glulisine) and 2.4–7.2 CV% (lispro). For glulisine, the lower limit of quantification (LLOQ) was set at 5.0 μU/ml, the upper limit of quantification (ULOQ) at 150 μU/ml. The respective values for lispro were 10.0 μU/ml (LLOQ) and 175 μU/ml (ULOQ).

Statistical Methods

PD parameters were derived from the individual GIR profiles, and PK parameters from the serum lispro and glulisine concentrations (INS). AUCs were calculated from untransformed data with the trapezoidal rule. Maximum insulin concentration (INS_{max}) and the time to INS_{max} (INS-T_{max}) were taken as observed, while maximum metabolic activity (GIR_{max}) and the time to GIR_{max} (GIR-T_{max}) were taken from GIR profiles smoothed with a weighted regression technique (procedure LOESS in SAS, SAS Institute, Cary, NC, USA). All PD parameters pertaining to GIR-AUCs as well as GIR_{max}, and all PK parameters pertaining to INS-AUCs as well as INS_{max}, were analysed (PK parameters after a natural log-transformation) using an analysis of variance model, which included insulin type, dose regimen, BMI group, period and sequence as main factors, a nested factor for subjects and interaction terms, to allow the estimation of least square (LS) means of interest.

For treatment comparisons, based on the LS means from this model, point estimates and corresponding 95% CI were calculated for either differences between parameters (PD) or ratios of parameters (PK). All time-related parameters [INS-T_{max}, GIR-T_{max}, 10% of total INS (INS-$t_{10\%}$), GIR-$t_{10\%}$] were subject to distribution-free (non-parametric) analyses (Wilcoxon signed-rank test). Point estimates (median) with corresponding 95% CI were calculated for the differences between treatment parameters.

The sample size in this study was based on the results of a previous trial [13] investigating the PD and PK properties of glulisine in obese, non-diabetic subjects with a BMI >30 kg/m^2 (mean BMI 34.7 kg/m^2). A sample size of 18 subjects per BMI group in that trial was estimated to give the study a power of >80% to detect a clinically significant difference between BMI groups for glulisine in onset of action at a significance level of $\alpha < 0.05$ in a double-sided comparison. Therefore, assuming a drop-out rate of approximately 10% per group, a sample size of 20 subjects per BMI group was chosen for this current study. Dropouts were only to be replaced if there were more than two dropouts in one BMI group. This sample size was larger than usual for PD/PK trials to ensure that even small differences in the PD/PK properties of glulisine between subjects with different BMIs were captured.

Results

Subjects

A total of 114 subjects were screened. Of these, 83 subjects met the inclusion criteria, were randomized, received at least one dose of study medication and were included in the safety analyses. Three subjects discontinued before study completion: one after receiving 0.4 U/kg glulisine because of adverse events possibly related to study medication (eyelid and peripheral oedema), one because of a protocol violation and one because of the person's own decision. According to the protocol, these subjects were replaced by three substitutes who received the same treatment sequence as the replaced subjects. In total, 80 subjects, distributed evenly between the BMI groups (20 subjects per group), were included in the PK and PD analyses. There were no relevant differences between the BMI groups with respect to age and gender distribution (table 1). The overall mean baseline BG value for the entire study population was 84 ± 7 mg/dl; baseline BG values were similar for all administered treatment sequences, with no major differences between the BMI groups.

Pharmacodynamics

Both analogues showed comparable overall glucodynamic efficacy (GIR-$AUC_{0-10\ h}$) (figure 1) and GIR_{max} at either dose (table 2). While GIR-T_{max} was comparable between the analogues, the onset of action was significantly faster for glulisine, as indicated by the significantly less time to achieve 10% of GIR-$AUC_{0-10\ h}$ (GIR-$t_{10\%}$) with glulisine, thus showing higher efficacy

Table 1 Baseline demographics

	BMI (kg/m^2)				
Variable	**All**	**<25**	**≥25 to <30**	**≥30 to <35**	**>35**
Male, n (%)	42 (52.5)	8 (40)	12 (60)	12 (60)	10 (50)
Female, n (%)	38 (47.5)	12 (60)	8 (40)	8 (40)	10 (50)
Age (years)	38.8 ± 9.8	37.6 ± 9.8	39.0 ± 9.4	39.7 ± 12.0	39.0 ± 8.4
Height (cm)	173.5 ± 8.9	171.5 ± 10.0	175.2 ± 6.9	175.1 ± 9.0	172.5 ± 9.2
Weight (kg)	91.6 ± 21.3	68.4 ± 11.9	83.2 ± 6.8	98.2 ± 9.8	116.6 ± 15.9
BMI (kg/m^2)	30.3 ± 6.4	23.1 ± 2.1	27.1 ± 1.3	32.0 ± 1.1	39.1 ± 3.5

Data are given as mean ± s.d., except for gender distributions.
BMI, body mass index.

in the first hour postdosing (GIR-AUC$_{0–1\ h}$; table 2). Correspondingly, the significantly greater ratio of GIR-AUC$_{0–1\ h}$/GIR-AUC$_{0–10\ h}$ with glulisine showed a significantly higher proportion of total metabolic activity occurring in the first hour postdosing for glulisine when compared with lispro (figure 2).

The faster onset of action with glulisine was not limited to any specific BMI group or to one dose. As shown in table 2 and figure 2, the PD parameters for onset of action showed significant differences between treatments for both 0.2 and 0.4 U/kg, and in nearly all BMI groups, although not all differences in the individual BMI groups reached statistical significance. However, no statistically significant ($p > 0.1$) interaction between insulin type and BMI group was observed for any PD parameter; thus, the observed differences were consistent across BMI subgroups.

Pharmacokinetics

The PK parameters derived from the lispro and glulisine concentrations for the total study population are listed in table 2. Higher maximum serum analogue concentrations and greater total area under the concentration time curves were measured with glulisine compared with lispro (for INS-AUC$_{0–10\ h}$ by approximately 40%; figure 1). However, because the total metabolic responses were comparable between treatments and the absolute bioavailabilities of glulisine and lispro are similar (approximately 70% [14,15]), the differences in insulin

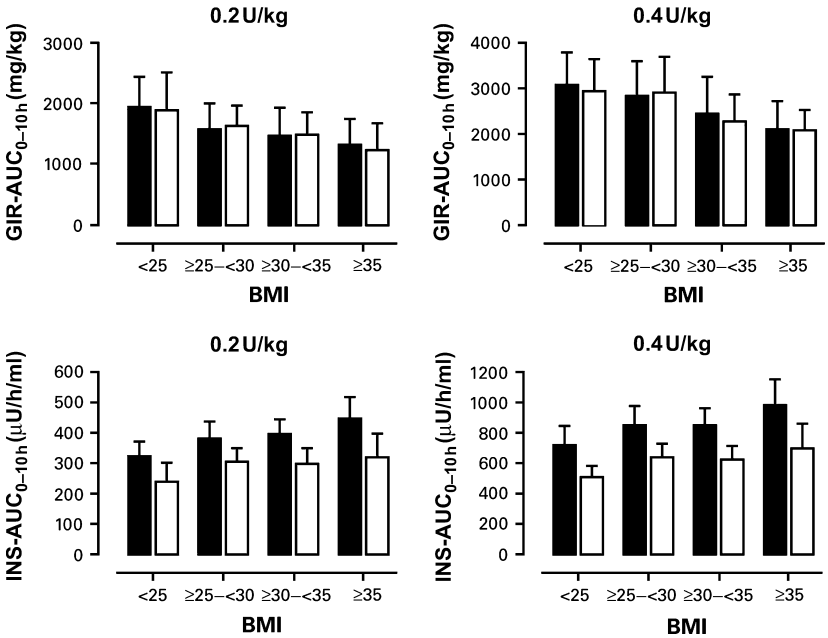

Fig. 1 Mean and s.d. for total glucose disposal (upper panel) and insulin exposure (lower panel) at 0.2 and 0.4 U/kg. Black bar = insulin glulisine; white bar = insulin lispro. BMI, body mass index; AUC, area under the curve; GIR, glucose infusion rate; INS, insulin.

Table 2 Pharmacodynamic and pharmacokinetic results

Variable	BMI (kg/m^2)	Insulin glulisine (0.2 U/kg)	Insulin lispro (0.2 U/kg)	Insulin glulisine (0.4 U/kg)	Insulin lispro (0.4 U/kg)
Pharmacodynamics					
GIR-AUC$_{0–10\ h}$ (mg/kg)	All	1569 ± 521	1554 ± 512	2564 ± 811	2459 ± 760
GIR-AUC$_{0–1\ h}$ (mg/kg)	All	102 ± 75*	83 ± 73	158 ± 100†	112 ± 71
$\frac{\text{GIR-AUC}_{(0–1\ h)}}{\text{GIR-AUC}_{(0–10\ h)}}$ (%)	All	6.4 ± 3.9†	5.1 ± 3.9	6.1 ± 3.3†	4.5 ± 2.6
	<25	9.8 ± 3.9	9.2 ± 4.6	9.2 ± 3.4†	7.0 ± 2.9
	≥25 to <30	6.8 ± 2.3†	4.8 ± 2.7	5.7 ± 2.0	4.5 ± 1.1
	≥30 to <35	4.9 ± 3.7*	3.6 ± 2.5	5.7 ± 3.2†	3.3 ± 2.1
	≥35	4.0 ± 2.9*	2.7 ± 1.8	3.7 ± 1.7	3.1 ± 1.7
GIR-t$_{10\%}$ (min)	All	83 ± 26*	87 ± 23	85 ± 20*	88 ± 18
GIR$_{max}$ (mg/kg/min)	All	5.8 ± 2.1	5.9 ± 2.6	8.4 ± 2.9	8.3 ± 3.0
GIR-T$_{max}$ (min)	All	190 ± 75	171 ± 53	196 ± 73	198 ± 65
Pharmacokinetics					
INS-AUC$_{0–10\ h}$ (μU/h.ml)	All	385 ± 69†	281 ± 68	842 ± 158†	603 ± 129
INS-AUC$_{0–1\ h}$ (μU/h.ml)	All	70 ± 24†	47 ± 22	135 ± 56†	84 ± 34
$\frac{\text{INS-AUC}_{(0–1\ h)}}{\text{INS-AUC}_{(0–10\ h)}}$ (%)	All	18.8 ± 7.4*	17.4 ± 8.8	16.6 ± 7.8†	14.5 ± 7.0
	<25	26.4 ± 6.7	27.4 ± 9.0	25.4 ± 8.0	22.6 ± 6.7
	≥25 to <30	19.9 ± 5.8*	17.1 ± 5.7	17.0 ± 4.7*	13.4 ± 3.8
	≥30 to <35	15.6 ± 5.6	14.0 ± 5.2	12.9 ± 5.3*	11.3 ± 5.5
	≥35	13.2 ± 3.5*	11.3 ± 4.8	10.9 ± 3.1	10.8 ± 4.5
INS-t$_{10\%}$ (min)	All	44 ± 11†	50 ± 14	49 ± 14†	54 ± 12
INS$_{max}$ (μU/ml)	All	115.2 ± 27.8*	95.9 ± 28.4	234.8 ± 68.5*	185.0 ± 51.7
INS-T$_{max}$ (min)	All	94 ± 42	76 ± 39	100 ± 40	92 ± 38

Data are given as mean ± s.d.

Test statistics were performed using an ANOVA model for the normally distributed pharmacodynamic parameters: GIR-AUC$_{0–1\ h}$, GIR-AUC$_{0–10\ h}$ and GIR$_{max}$. The pharmacokinetic parameters INS-AUC$_{0–1\ h}$, INS-AUC$_{0–10\ h}$ and INS$_{max}$ were analysed with the same ANOVA model after a natural log-transformation. All time-related parameters (INS-T$_{max}$, GIR-T$_{max}$, INS-t$_{10\%}$, GIR-t$_{10\%}$) were tested with non-parametric analyses (Wilcoxon signed-rank test). Please refer to the Statistical Methods for further details.

ANOVA, analysis of variance; BMI, body mass index; AUC, area under the curve; GIR, glucose infusion rate; GIR-t$_{10\%}$, time to 10% of GIR-AUC$_{0–10\ h}$; GIR$_{max}$, maximum GIR; GIR-T$_{max}$, time to GIR$_{max}$; INS, insulin; INS-t$_{10\%}$, time to INS-AUC$_{0–10\ h}$; INS$_{max}$, maximum INS concentration; INS-T$_{max}$, time to INS$_{max}$.

*$p < 0.05$; †$p < 0.001$ vs. corresponding insulin lispro/BMI group.

exposure are considered artefactual and are because of differences in the cross-reactivity to human insulin between the analogue-specific kits used for analysis. Taking this into consideration, the PK parameters explain the PD findings. The absorption of glulisine was significantly faster than that of lispro in the total study population, indicated by the lesser time required to achieve early exposure with glulisine (INS-t10% approximately 5–6 min less), resulting in a greater INS-AUC0–1 h/INS-AUC0–10 h ratio (table 2; figure 2). The difference in INS-t$_{10\%}$ was statistically significant across the BMI ranges with both doses; except for 0.4 U/kg in morbidly obese subjects (figure 1). The difference in INS-t$_{20\%}$ also tended to be in favour of glulisine ($p = 0.058$ for 0.2 U/kg and $p = 0.151$ for 0.4 U/kg), although this did not translate into significant differences in GIR-t$_{20\%}$. Moreover, insulin exposure (INS-AUC$_{0–10\ h}$ and INS$_{max}$) increased as BMI increased, while glucose disposal (GIR-AUC$_{0–10\ h}$ and GIR$_{max}$) decreased with both insulin analogues (figure 1).

There were no significant differences in mean C-peptide concentrations between glulisine and lispro (data not shown). No relevant increases above baseline levels were observed in any of the clamps for this variable with either treatment, indicating that the study results were not influenced by changes in endogenous insulin secretion.

No relevant changes in the safety laboratory variables and no serious adverse events were observed with either treatment or dose, apart from decreases in erythrocyte, haemoglobin and haematocrit measurements, which were attributed to the frequent blood sampling during the study.

Discussion

This study compared the pharmacological properties of the two fast-acting insulin analogues, glulisine and lispro in subjects without diabetes, over a wide BMI range. Two different doses were used in this study, 0.2 U/kg as a standard dose and 0.4 U/kg as a high dose. Both analogues showed comparable overall glucodynamic efficacy

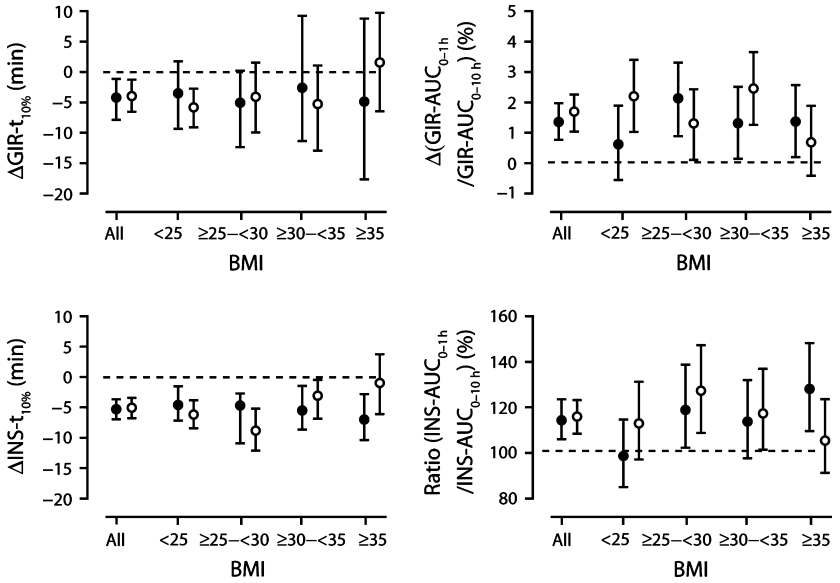

Fig. 2 Point estimates with 95% confidence limits for pharmacodynamic (upper panel) and pharmacokinetic (lower panel) parameters. Black circles = 0.2 U/kg; white circles = 0.4 U/kg. The plots show differences between insulin glulisine and insulin lispro or the ratio of insulin glulisine over insulin lispro. BMI, body mass index; AUC, area under the curve; GIR, glucose infusion rate; GIR-$t_{10\%}$, time to 10% of GIR-$AUC_{0–10\ h}$; INS, insulin; INS-$t_{10\%}$, time to INS-$AUC_{0–10\ h}$.

(GIR-$AUC_{0–10\ h}$), GIR-T_{max} and GIR_{max} at either dose. However, as shown by the greater ratio of GIR-$AUC_{0–1\ h}$/GIR-$AUC_{0–10\ h}$ with glulisine, a significantly higher proportion of total metabolic activity occurred in the first hour postdosing for glulisine compared with lispro (figure 2). This is also reflected in the higher efficacy in the first hour postdosing (GIR-$AUC_{0–1\ h}$) and accompanied by a faster onset in activity shown by significantly reduced GIR-$t_{10\%}$ with glulisine.

This finding confirms the observations of a previous glucose clamp study performed in obese subjects without diabetes, with a BMI of 30–40 kg/m^2, which also reported a faster rise in insulin concentration and a faster onset of action with glulisine than with lispro [13]. The present study with 320 euglycaemic glucose clamp experiments expands these findings to subjects with a BMI range of 20–40 kg/m^2. As no treatment by BMI interaction was shown for any PD parameter ($p > 0.1$), the statistical significance of these treatment differences established for the total study population can be generalized, i.e. the earlier onset of action of glulisine occurs in both lean and obese (and even morbidly obese) subjects.

Fast-acting insulin analogues have been compared for differences in PD and PK properties for clinical implications soon after their advent. For instance, Hedman *et al.* reported a faster rise and an earlier decline in insulin concentrations with lispro compared with aspart [16]. These differences in PK properties, observed in 14 patients with type 1 diabetes were not, however, accompanied by any differences in postprandial BG concentrations after a standard meal. Furthermore, other studies with more patients [17] or more complex methods [18] did not show any significant differences (in either PK or PD) between aspart and lispro. Thus, our confirmation of previous findings [13] of the faster onset of action of glulisine vs. lispro might be surprising, but may be because of the absorption processes of both insulins. The drug formulation of glulisine differs from those of lispro and aspart; glulisine is stable with polysorbate 20, whereas the other analogues need to be formulated with zinc [19]. Zinc is added to stabilize insulin molecules in hexamers (with two zinc atoms located in the centre of the hexamer) to achieve a practical shelf life [20]. Although lispro is more rapidly absorbed from pure monomeric solution compared with hexameric lispro (the prevalent form in the commercially available product), it lacks sufficient shelf life and in-use stability [15,21]. The oligomeric aggregates of glulisine molecules in solution are adequately stable without zinc, presumably because of the unaltered proline at position B28 allowing dimerization [22,23]. Thus, it is plausible to attribute the observed moderate disparity in early absorption and metabolic action between glulisine and lispro to differences in the association status of the insulin molecules. This is linked to the physicochemical properties of their formulations.

As the difference between glulisine and other fast-acting analogues manifests in the zinc-free formulation of glulisine, the faster onset of action should be evident in all subjects (subjects without diabetes, subjects with type 1 or type 2 diabetes, lean or obese subjects). The fact that such a difference between glulisine and lispro was not observed in a previous study in subjects with type 2 diabetes [7] is probably because of the insufficient power of that study, which used an incomplete block design and thereby increased the variability between the treatment groups studied.

The imminent question regarding the clinical relevance of the observed faster onset of action of glulisine is a difficult one. While being statistically significant, the absolute difference, although small (e.g. INS-$t_{10\%}$ differed only by 5–6 min), afforded a 25–30% greater glucose disposal within the first hour after injection. In a previous study, the difference in the onset of action (expressed as the time to reach half-maximal activity) between aspart and RHI was reported to be not more than 13 min [24], indicating that the onset of action of glulisine might be meaningfully faster than that of the other fast-acting analogues. The clinical relevance of such findings has to be shown in adequately designed clinical studies. The only clinical study available so far with a head-to-head comparison between glulisine and lispro was conducted in patients with type 1 diabetes and did not show any difference in glycated haemoglobin or incidence of hypoglycaemic events between the analogues [25]. However, less basal insulin was required with glulisine as compared with lispro. This adds to the conclusion that improved PK/PD properties of new prandial insulins need to be accompanied by adaptations in the basal insulin regimen before leading to an improvement in overall metabolic control [6].

While the faster onset of action of glulisine was evident in all BMI subgroups in this study, it might be of highest clinical relevance in obese subjects. Previous findings report significantly delayed absorption in obese subjects [10,11], and a negative correlation of absorption and action with fat layer thickness for s.c. injection of RHI [26,27]. We observed a modest decrease in INS-$AUC_{0–1\ h}$/INS-$AUC_{0–10\ h}$ ratio (figure 2) at increasing total absorption, INS-$AUC_{0–10\ h}$ (figure 1), with increasing BMI. Nevertheless, insulin resistance, a characteristic feature of obesity [28], is closely associated with the amount of visceral fat [26,29,30], and leads to an attenuation of the metabolic activity of any insulin product, as also shown in this study for both glulisine and lispro.

Thus, both attenuated absorption and reduced metabolic activity have to be accounted for in obese people because the time–action profile of s.c. RHI is shifted to the right and shows less peak activity compared with lean subjects. For these patients, it may be of particular importance to use the insulin analogue with the most rapid onset of action to counteract the right-shift in the insulin time–action profiles.

In conclusion, our study confirms previous observations of a faster onset of action of glulisine as compared with lispro. This faster onset of action of glulisine, which is associated with the novel drug formulation, is evidently independent of the insulin dose and the subjects' BMI.

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