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Insulin glulisine, insulin lispro and regular human insulin show comparable end-organ metabolic effects: an exploratory study

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Aims: To compare the end-organ metabolic effects of insulin glulisine (glulisine), insulin lispro (lispro) and regular human insulin (RHI) in patients with type 1 diabetes mellitus.
Methods: Eighteen patients with type 1 diabetes mellitus (mean age 36.9 ± 8.6 years, BMI 23.6 ± 2.8 kg/m^2, haemoglobin A_{1c} 7.4 ± 0.9%) were randomized in this single-centre, double-blind, three-period cross-over, standard Latin-square, euglycaemic glucose clamp trial. Patients received sequential, primed stepwise intravenous infusions of glulisine, lispro or RHI (infusion rates were increased in a stepwise manner from an initial rate of 0.33 [180 min] to 0.66 [180 min] and 1.00 [180 min] mU/kg/min). The primary variables were the suppression of endogenous glucose production (S_{EGP}) and glucose uptake (GU).
Results: Mean basal endogenous glucose production (EGP) was 1.88, 2.12 and 2.12 mg/kg/min for glulisine, lispro and RHI respectively. Mean (±s.e.) maximum absolute S_{EGP} (adjusted for basal EGP) was −1.64 ± 0.06, −1.72 ± 0.05 and −1.56 ± 0.05 mg/kg/min respectively. Mean (±s.e.) maximum absolute increase in GU (adjusted for basal GU) was 6.46 ± 0.26, 6.23 ± 0.24 and 6.72 ± 0.24 mg/kg/min respectively. There were no clinically relevant differences between the three insulin treatments with respect to serum insulin, free fatty acid (FFA), glycerol or lactate levels. No serious adverse events and no episodes of severe hypoglycaemia were reported.
Conclusions: This study shows that glulisine, lispro and RHI have similar effects on S_{EGP}, GU, FFA, glycerol and lactate levels, providing evidence for similar end-organ metabolic effects.
Keywords: euglycaemic glucose clamp, glulisine, lispro
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Introduction

The Diabetes Control and Complications Trial demonstrated the benefits of tight glycaemic control with respect to improving long-term outcomes in patients with type 1 diabetes mellitus [1]. Basal–bolus insulin therapy is essential in patients with type 1 diabetes mellitus to achieve near-normoglycaemic blood glucose levels and reduce the risk of long-term clinical complications [1].

Insulin therapy should mimic the absent physiological insulin secretion, combining a postprandial peak in plasma insulin with a continuous basal insulin profile [2,3]. However, attempts to copy the physiological pattern of insulin secretion have been hampered by the variable absorption and inappropriate time–action profiles of subcutaneously applied insulin [4–9]. Regular human insulin (RHI), which has traditionally been used for postprandial glycaemic control, does not sufficiently

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mimic the time–action profile of endogenous insulin to fulfil either basal or bolus insulin requirements [10]. Therefore, long-acting insulin analogues (such as once-daily insulin glargine), intermediate-acting and long-acting formulations (such as twice-daily NPH insulin and ultralente) and rapid-acting insulin analogues [such as insulin glulisine (glulisine) and insulin lispro (lispro)] have been developed to provide a more physiological insulin supply and thus improve glycaemic control.

Glulisine is a new rapid-acting insulin analogue that was developed to fulfil mealtime (bolus) insulin requirements in patients with diabetes, with a more rapid onset and shorter duration of action compared with RHI [11–13]. In patients with type 2 diabetes mellitus, glulisine statistically significantly reduces haemoglobin A_{1c} (HbA_{1c}) compared with RHI, with no increase in hypoglycaemic episodes [14]. In patients with type 1 diabetes mellitus, glulisine provides similar glycaemic control and safety to lispro [15].

However, studies have suggested differences between glulisine and other short- or rapid-acting insulin preparations in terms of end-organ metabolic effects and insulin signalling [16]. Furthermore, inhibitions of cytokine and fatty acid–induced beta cell deaths have been described *in vitro* and interpreted as an enhanced anti-apoptotic activity of glulisine, which may reflect the unique property of glulisine to predominantly activate the insulin receptor substrate-2 signalling pathway [16]. Glulisine has been shown to better maintain rapid-acting properties than lispro in patients with obesity [17], which may be because of its differing pharmacodynamic aspects.

These findings hint at differences between glulisine, lispro and RHI, which, as we hypothesised, may be because of different effects on endogenous glucose production (EGP). To explore this hypothesis, the present study was conducted to compare the end-organ metabolic effects of glulisine with lispro and RHI in patients with type 1 diabetes mellitus.

Methods

Patients

Eighteen patients with type 1 diabetes mellitus (male and female) aged 18–70 years, with HbA_{1c} levels $\leq$10%, BMI $<$30 kg/m^2 and fasting C-peptide levels $<$0.05 nmol/l, participated. All subjects had to have been diagnosed with diabetes for $\geq$2 years and treated with intensified insulin therapy for $\geq$3 months. Three patients were on continuous subcutaneous insulin infusion treatment (CSII). Important exclusion criteria included patients who had experienced recurrent severe hypoglycaemia or hypoglycaemic unawareness (as judged by the investigator), total daily insulin dose $\geq$1.4 IU/kg, signs of hepatic or renal disease (as indicated by elevated levels of alanine aminotransferase, alkaline phosphatase $\geq$2 times and/or creatinine $\geq$1.5 times the upper limit of the normal reference range for the age group) and serum insulin antibody levels $>$20 U/ml determined at screening.

Study Design

This euglycaemic glucose clamp trial followed a single-centre, randomized, double-blind, three-period cross-over, standard Latin-square design. The protocol was reviewed and approved by the local ethics committee in Graz, Austria, and the trial performed in accordance with Good Clinical Practice and the Declaration of Helsinki.

Study Protocol

The study comprised three trial periods (a screening visit [visit 1], three treatment days [visits 2–4] and a follow-up visit [visit 5]; figure 1A). The three treatment days consisted of primed, stepwise, intravenous infusions of either (A) glulisine, (B) lispro or (C) RHI at infusion rates increasing in a stepwise manner from an initial rate of 0.33 (low dose) to 0.66 (medium dose) to 1.00 mU/kg/min (high dose). Treatment randomizations occurred at visit 2 and followed a three-sequence, three-period Latin-square design (i.e. ABC, BCA, CAB).

Each study day lasted from the patient's arrival in the clinic at about 07:00 hours until approximately 22:00 hours. Patients arrived at the clinic in the morning of visits 2, 3 and 4 having fasted overnight (except for water) from at least midnight the evening before, and without having taken any insulin in the morning, except for subjects on CSII, who were to leave the pump running at the basal rate.

Euglycaemic clamps combined with a tracer dilution technique using D-[6,6-$^2H_2$]-labelled glucose were used to determine EGP and whole-body glucose uptake (GU) [18]. Between 07:00 and 07:30 hours, a vein in the patient's hand or forearm was cannulated and the hand kept in a thermoregulated box for sampling of arterialized venous blood. A catheter was inserted into an antecubital vein on the contralateral arm for infusion of insulin and/or glucose. Around 08:00 hours (−240 min), a variable intravenous infusion of unmodified human insulin (0.4 IU/ml) was started in order to establish euglycaemia at a plasma glucose level of 5.0 mmol/l, range 3.9–6.1 mmol/l (90 mg/dl, range 70–110 mg/dl). Adjustments of the basal insulin infusion rate were allowed until steady-state conditions were reached; this

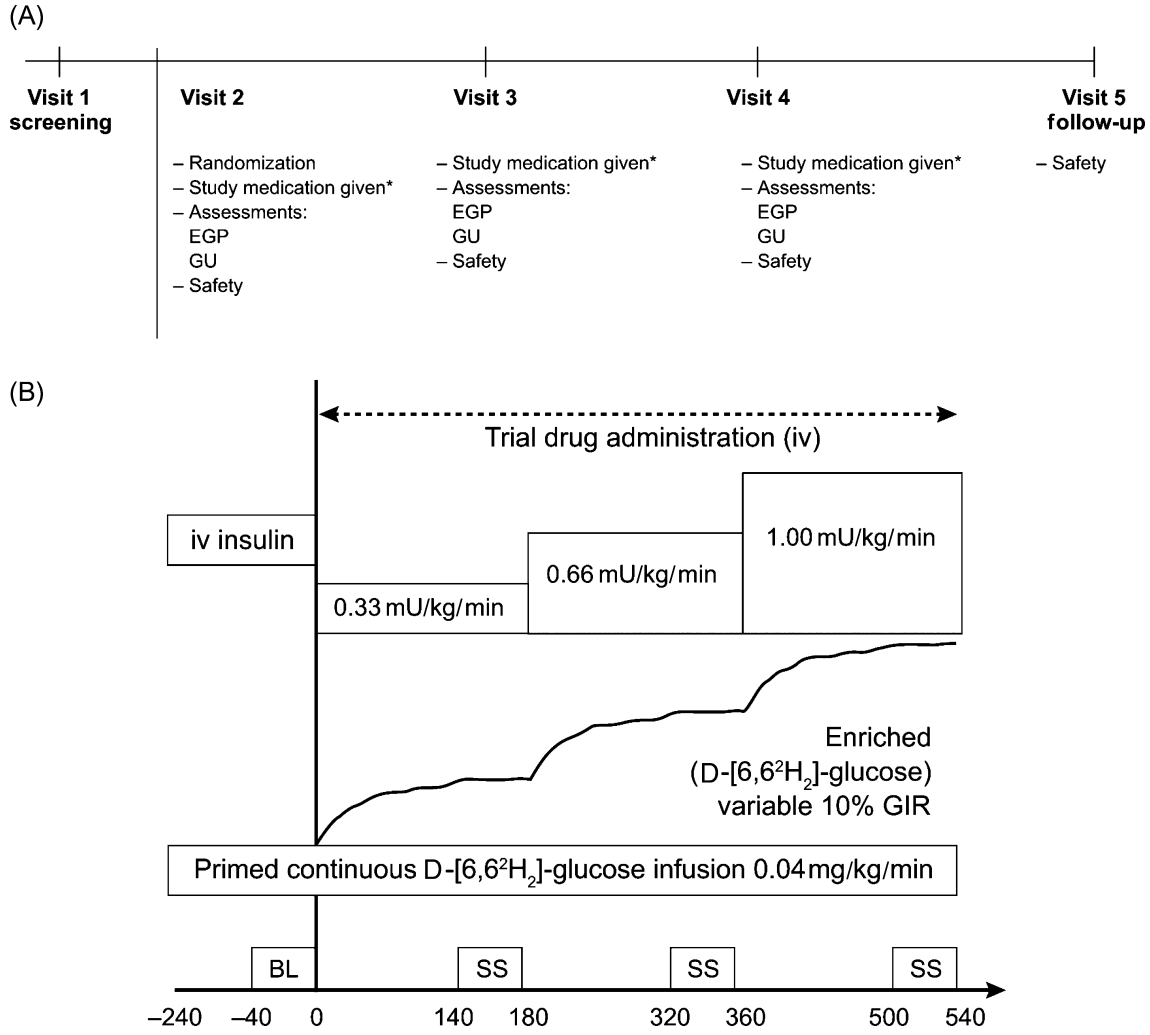

Fig. 1 Study design (A) and schedule for clamp procedure (B). *Three study medications administered to each subject during the study: one medication per visit, at visits 2, 3 and 4. The sequence of administration of study medication at visits 2–4 varied according to the randomization schedule. EGP, endogenous glucose production; GU, glucose uptake. BL, baseline; GIR, glucose infusion rate; iv, intravenous; SS, steady state.

infusion rate remained unchanged for 40 min [19]. A primed continuous infusion of D-[6,6-$^2H_2$]-glucose was started at approximately 08:00 hours with an adjusted priming dose of 4.8 mg/kg D-[6,6-$^2H_2$]-glucose infused over 1 min, followed by a constant infusion of 0.04 mg/kg/min D-[6,6-$^2H_2$]-glucose, which was carried forward throughout the whole experiment [20]. When steady glucose levels (baseline: time −40 to 0 min) were established (at around 12:00 hours [time point 0 min]), the infusion with unmodified human insulin was withdrawn and immediately replaced by intravenous trial drug administration, starting with an 0.33 mU/kg/min infusion rate for the first 3 h (time 0–180 min). Also at time 0, a variable intravenous glucose infusion (10% glucose, enriched with 1 g D-[6,6-$^2H_2$]-glucose/500 ml) was started in order to maintain plasma glucose levels at 5.0 mmol/l (range 3.9–6.1 mmol/l). The enrichment with 1 g D-[6,6-$^2H_2$]-glucose/500 ml was to prevent a fall in tracer enrichment and consequent errors in glucose turnover determination, which can otherwise occur after insulin administration. The glucose infusion continued until the end of the study day to maintain euglycaemic conditions. After 3 h, the infusion rate of the trial drug was sequentially increased to 0.66 mU/kg/min for the following 3 h (time 180–360 min) and to 1.00 mU/kg/min for a further 3-h period (time 360–540 min). To ensure the desired plasma insulin concentrations within the 3-h periods, an adjusted intravenous insulin

bolus of the trial drug was employed at time 0, time 180 min and time 360 min. The three treatment days were separated by a washout period of 5–21 days. The follow-up visit was performed up to 7 days after the last treatment visit (figure 1B).

Primary and Secondary Objectives

The primary objective of the study was to compare the effect of glulisine, lispro and RHI on the suppression of endogenous glucose production (S_{EGP}) during euglycaemic glucose clamps using stable, labelled glucose in patients with type 1 diabetes mellitus. The secondary objectives were to assess the effect of glulisine, lispro and RHI on free fatty acids (FFA), lactate and glycerol levels and the safety and tolerability of glulisine in comparison to lispro and RHI.

Pharmacokinetic Assessments

Serum insulin concentration time profiles were used to calculate pharmacokinetic variables from blood samples collected at −240 min and at baseline (−40, −30, −20, −10 and 0 min) and after study drug administration at 20- to 30-min intervals, except at steady state (last 40 min of each 3-h dosing interval), when samples were collected every 10 min (140–180, 320–360 and 500–540 min).

Pharmacodynamic Assessments

The primary analysis variable was the S_{EGP}, calculated as the absolute change in EGP from basal steady state (from −40 to 0 min before start of study drug administration) to the EGP during each of the three later steady-state levels. The pharmacodynamic data collected were glucose infusion rates (GIR), blood glucose concentrations and plasma levels of FFA, lactate and glycerol. Sampling times for FFA, lactate and glycerol were as described for the pharmacokinetic data. The primary derived pharmacodynamic variables were EGP and whole-body GU [both rate per minute standardized for body weight (kg at screening)].

Safety Assessments

Safety was assessed in terms of laboratory safety (haematology, biochemistry and urinalysis), physical examinations, electrocardiograms and vital signs. Laboratory safety tests and physical examinations were performed at visits 1 and 5, apart from hepatitis screenings, diabetes characterisation and ferritin measurements, which were only performed at visit 1. Blood glucose and potassium levels were measured additionally at visits 2–4, and vital signs were recorded at every visit.

Sample Analysis

Concentrations of serum insulin were analysed using a radioimmunoassay with a glulisine standard calibration curve for glulisine samples and a human insulin standard calibration curve for lispro or RHI. The lower limit of quantification was 5.0 μU/ml for free glulisine and 4.3 μU/ml for free immunoreactive insulin. Plasma glucose was analysed based on an oxygen rate method on a Beckman Analyzer 2 (Beckman Instruments Inc., Fullerton, CA, USA). For the simultaneous measurement of glucose and D-[6,6-$^2H_2$]-glucose, samples were analysed using gas chromatography–mass spectrometry [18,21]. Enzymatic kits were used on a Cobas Mira (Roche Diagnostics, Basel, Switzerland) to analyse samples for FFA (Wako, Neuss, Germany), lactate (Roche Hitachi, Mannheim, Germany) and glycerol (Sigma, Missouri, USA).

Statistics

The evaluable population consisted of all subjects who received study medication and completed the study; the pharmacodynamic analysis was performed on those subjects from the evaluable population whose data from visits 2–4 were considered viable. The analysis was not performed on an intention-to-treat basis.

Statistical tests were performed as two-sided tests with $\alpha = 0.05$. Because of the exploratory nature of the trial, no adjustment of the error levels because of multiple testing was performed. For the pharmacokinetic analysis, individual ratios of the individual geometric mean serum insulin concentrations were calculated and summary statistics generated. Ratios were derived with the highest infusion rate as the reference dosage. An analysis of variance (ANOVA) model was used to examine the null hypothesis of no difference in S_{EGP} between the three treatment groups in the evaluable population. The model included fixed effects for insulin, period, sequence and patient within sequence. From this ANOVA model, 95% two-sided confidence limits for treatment effects were generated, as well as p values for pairwise contrasts for glulisine vs. lispro and RHI. In addition, analysis of covariance (ANCOVA) models including the corresponding baseline value of the various individual pharmacodynamic variable as a covariate (model I) were used to examine the null hypothesis of no difference in the corresponding pharmacodynamic variable. Safety analyses were performed on the safety population defined as all subjects who received study medication. For safety variables, p values were exploratory only (because of small

patient numbers) and calculated using a two-sided, exact unconditional (McNemar) test for equality of two related binomial proportions.

Results

Patient Conduct

This study screened 26 patients with type 1 diabetes mellitus, 18 of whom were randomized. Seven of the 26 patients failed screening because of insulin antibody levels >20 U/ml and one because of high antibody levels (>20 U/ml) and alkaline phosphatase levels that were twice the upper limit of the normal reference range. The first subject was enrolled on 14 April 2004, and the last subject completed the study on 25 May 2004. Six patients were randomized to the treatment sequence ABC, six were randomized to the sequence BCA and six to the sequence CAB (where A = glulisine, B = lispro and C = RHI). All 18 randomized patients completed the study; however, one patient (no. 0015) had incomplete pharmacodynamic data on the last clamp visit and was thus not evaluable for the pharmacokinetic and pharmacodynamic analyses. There were no major protocol violations.

Baseline Characteristics

Demographic data were comparable across the randomized groups (treatment sequences): total 17 patients; 70.6% male; 100% Caucasian; mean age (±s.d.) 36.6 ± 8.8 years; BMI 23.6 ± 2.9 kg/m^2; HbA_{1c} 7.3 ± 0.9%.

Endogenous Glucose Production

Individual geometric mean serum insulin concentrations at steady state were comparable between treatments for each of the three infusion rates (doses). The ratios of concentrations for dosage steps (low/high and middle/high) were also comparable between treatment groups and were, for each treatment, close to the one-third and two-third fractions of the 1.00 mU/kg/min, respectively, indicating dose proportionality (figure 2A).

EGP was suppressed at all dosage levels with glulisine, lispro and RHI (table 1). For all insulins, S_{EGP} was substantially higher at 0.66 and 1.00 vs. 0.33 mU/kg/min; however, a dose increase from 0.66 to 1.00 mU/kg/min did not suppress EGP much further (table 1 and figure 2B). Comparison of basal EGP values (least square means) showed statistically significant differences between insulin treatments and overall (p = 0.02; glulisine vs. lispro: p = 0.01; glulisine vs RHI: p = 0.01). The highest level of suppression according to the arithmetic means

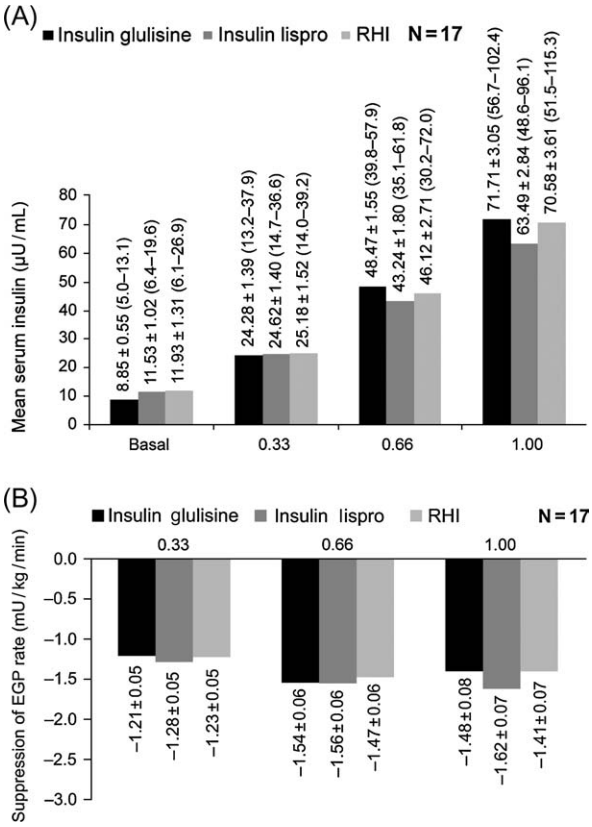

Fig. 2 (A) Individual geometric means of serum insulin in the steady-state phase (data are mean ± s.e. [min − max]) and (B) suppression of endogenous glucose production (least squares mean) adjusted for baseline EGP (data are mean ± s.e.). RHI, regular human insulin; EGP, endogenous glucose production.

was achieved with lispro at all dosage levels. At the highest dosage levels, the arithmetic mean S_{EGP} was −1.3 mg/kg/min for glulisine, −1.7 mg/kg/min for lispro and −1.5 mg/kg/min for RHI. A highly significant effect of the covariate 'basal EGP' on the outcome (S_{EGP}) could be observed from the corresponding ANCOVA analysis (model I). When adjusted for basal EGP, there were no differences between glulisine and lispro or between glulisine and RHI at any dosage level (table 1). To better understand clinically relevant differences in absolute EGP values, the individual three basal values (before application of the different insulins) for EGP within one patient were compared. The mean of the maximal differences of the basal values was 0.5 mg/kg/min, and the range was 0.135–1.075 mg/kg/min (data not shown).

Glucose Uptake

There was a stepwise increase in GU with the increasing insulin infusion rates. Mean (±s.e.) maximum absolute

Table 1 Pharmacodynamic data for glulisine, lispro and regular human insulin

		Least square mean			Glulisine vs. lispro			Glulisine vs. RHI		
Variable	Infusion rate (mU/kg/min)	Glulisine	Lispro	RHI	Mean difference (treatment effect)	95% CI	p value	Mean difference (treatment effect)	95% CI	p value
EGP (mg/kg/min)	Basal	1.88	2.12	2.12	—	—	0.01	—	—	0.01
ANCOVA model I*										
Maximum S_{EGP} (mg/kg/min)	Overall	−1.64	−1.72	−1.56	0.080	−0.087, 0.248	0.34	−0.076	−0.243, 0.090	0.36
S_{EGP} (mg/kg/min)	0.33	−1.21	−1.28	−1.23	0.066	−0.079, 0.211	0.36	0.017	−0.127, 0.161	0.81
	0.66	−1.54	−1.56	−1.47	0.018	−0.162, 0.198	0.84	−0.065	−0.244, 0.114	0.46
	1.00	−1.48	−1.62	−1.41	0.134	−0.097, 0.365	0.24	−0.071	−0.301, 0.158	0.53
% S_{EGP}	0.33	−59.2	−62.5	−60.4	3.314	−3.357, 9.985	0.32	1.149	−5.495, 7.793	0.73
	0.66	−75.1	−76.4	−70.9	1.234	−8.168, 10.635	0.79	−4.215	−13.579, 5.149	0.37
	1.00	−71.7	−78.4	−67.9	6.674	−4.500, 17.848	0.23	−3.851	−14.980, 7.279	0.49
Maximum GU (mg/kg/min)	Overall	6.46	6.23	6.72	0.230	−0.512, 0.971	0.53	−0.252	−1.012, 0.508	0.50
GU (mg/kg/min)	0.33	1.12	1.25	1.29	−0.129	−0.654, 0.396	0.62	−0.173	−0.711, 0.365	0.52
	0.66	4.30	4.43	4.59	−0.132	−0.968, 0.704	0.75	−0.292	−1.149, 0.564	0.49
	1.00	6.43	6.18	6.72	0.250	−0.519, 1.018	0.51	−0.295	−1.082, 0.493	0.45

Overall p value for between-treatment differences in basal EGP = 0.02.
*ANCOVA model I adjusted for basal EGP values. RHI, regular human insulin; CI, confidence interval; EGP, endogenous glucose production; ANCOVA, analysis of covariance; GU, glucose uptake; S_{EGP}, suppression of endogenous glucose production.

increase of GU (adjusted for basal GU) was 6.46 ± 0.26, 6.23 ± 0.24 and 6.72 ± 0.24 mg/kg/min for glulisine, lispro and RHI respectively. During the clamp, serum insulin and blood glucose concentrations and GIR were comparable for all insulins.

FFAs and Glycerol Levels

There were no clinically relevant differences between the three insulin treatments with respect to FFA or glycerol (table 2). In general, FFA and glycerol decreased with increasing insulin doses. The magnitudes of the changes from basal levels for FFA and glycerol were largely the same when comparing the doses of 0.66 and 1.00 mU/kg/min, indicating that the high dose did not cause a change much greater than the middle dose.

Plasma Lactate Levels

There were no clinically relevant differences between the three insulin treatments with respect to plasma lactate levels (table 2). In general, lactate increased with increasing insulin doses.

Safety

No clinically relevant changes over the course of the study were observed for laboratory safety data, physical examinations, electrocardiograms or systolic and diastolic blood pressure. Changes in pulse rate were recorded for one patient on glulisine, one on lispro and two patients on RHI although the investigator did not consider these to be a matter for concern.

Discussion

This study compared the effects of glulisine, lispro and RHI on EGP in patients with type 1 diabetes mellitus, employing the euglycaemic hyperinsulinaemic clamp technique and stepwise dose increases. Literature addressing the effects of different insulins, particularly with regards to bolus insulin and normal variability on EGP, peripheral glucose disposal and their end-organ metabolic effects when administered intravenously, is currently very limited. For this reason, the three individual basal values (before application of the different insulins) for EGP within one patient were compared in order to enhance the ability of interpreting clinically relevant differences in absolute EGP values.

Our results showed that glulisine, lispro and RHI have a similar effect on S_{EGP} and on GU when administered by continuous stepwise intravenous infusion in patients with type 1 diabetes mellitus. The maximum absolute difference in the mean S_{EGP} between insulin treatments was 0.400 mg/kg/min for glulisine vs. lispro at the high dose (p = 0.008), a difference without clinical relevance.

Table 2 Changes in plasma FFAs, glycerol and lactate

		Least square mean change			Glulisine vs. lispro			Glulisine vs. RHI		
Variable	Infusion rate (mU/kg/min)	Glulisine	Lispro	RHI	Mean difference (treatment effect)	95% CI	p value	Mean difference (treatment effect)	95% CI	p value
FFA (mmol/l)	Basal	0.23	0.28	0.23	—	—	0.25	—	—	0.88
Glycerol (mg/l)	Basal	3.01	3.62	3.13	—	—	0.09	—	—	0.72
Lactate (mg/dl)	Basal	7.00	7.66	6.93	—	—	0.28	—	—	0.91
ANCOVA model I*										
FFA (mmol/l)	0.33	−0.12	−0.19	−0.09	0.070	−0.000, 0.141	0.05	−0.032	−0.101, 0.037	0.35
	0.66	−0.21	−0.23	−0.23	0.017	0.000, 0.033	0.05	0.013	−0.003, 0.029	0.11
	1.00	−0.23	−0.23	−0.23	0.001	−0.011, 0.013	0.83	−0.000	−0.012, 0.011	0.94
Glycerol (mg/l)	0.33	−0.98	−1.38	−0.60	0.402	−0.243, 1.047	0.21	−0.378	−0.994, 0.237	0.22
	0.66	−1.06	−1.34	−1.21	0.281	−0.126, 0.688	0.17	0.147	−0.241, 0.535	0.45
	1.00	−1.14	−1.35	−1.28	0.215	−0.126, 0.557	0.21	0.148	−0.178, 0.474	0.36
Lactate (mg/dl)	0.33	−0.46	−0.30	−0.47	−0.163	−0.948, 0.621	0.67	0.008	−0.761, 0.778	0.98
	0.66	2.69	3.73	2.51	−1.043	−2.242, 0.156	0.09	0.177	−0.999, 1.352	0.76
	1.00	5.37	4.17	4.78	1.200	0.120, 2.280	0.03	0.596	−0.463, 1.654	0.26

Overall p values for between-treatment differences in basal values of FFA = 0.45; glycerol = 0.20; lactate = 0.41.
*ANCOVA model I adjusted for basal values. FFA, free fatty acids; CI, confidence interval; ANCOVA, analysis of covariance.

Although the basal EGP for the three treatment arms was within the expected range (1.88–2.12 mg/kg/min), there were, however, significant between-treatment differences in basal EGP (p = 0.02 overall; p = 0.01 between glulisine and lispro). These differences may be because of the variability of the method used; therefore, a correction was made for the baseline EGP. After adjustment for basal EGP, S_{EGP} was comparable between all three insulin treatments. The maximum absolute difference in mean S_{EGP} between glulisine and lispro at the high dose was 0.134 mg/kg/min (p = 0.244) after adjustment for basal EGP, which was neither statistically nor clinically relevant.

A stepwise increase in GU occurred with increasing insulin infusion rates (doses) of the three insulin treatments; the greatest increase was achieved with glulisine at all insulin infusion rates. After adjustment for basal GU (model 1 ANCOVA), the differences between the insulin treatments were neither statistically significant nor clinically relevant at any dosage level. There were no clinically relevant differences between the three insulin treatments with respect to FFA, glycerol or lactate levels, indicating similar metabolic activity for all three insulins. Glulisine, lispro and RHI were safe and well tolerated, reflecting results seen in previous studies [22–24].

In conclusion, this exploratory study suggests that intravenous glulisine, lispro and RHI show similar effects on S_{EGP}, GU, FFA, glycerol and lactate in patients with type 1 diabetes mellitus, indicating that glulisine has similar end-organ metabolic effects to other rapid- and short-acting insulins. Together with results from other studies [25], this study provides evidence for physiological signalling and safe use of glulisine in patients with type 1 diabetes mellitus. As this is an exploratory study, further confirmatory studies will be needed for conclusive statements.

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