A Direct Comparison of Insulin Aspart and Insulin Lispro in Patients With Type 1 Diabetes

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OBJECTIVE — Both rapid-acting insulin analogs, insulin aspart and lispro, attenuate prandial glucose excursion compared with human soluble insulin. This trial was performed to study the pharmacokinetic and pharmacodynamic profiles of insulin aspart and insulin lispro in type 1 diabetic patients in a direct comparison and to investigate whether the administration of one analog results in favorable effects on prandial blood glucose control.

RESEARCH DESIGN AND METHODS — A total of 24 type 1 diabetic patients (age 36 ± 8 years, 16 men and 8 women, BMI 24.3 ± 2.6 kg/m^2, diabetes duration 17 ± 11 years, HbA_{1c} 7.9 ± 0.8%) on intensified insulin therapy were recruited into a single-center, randomized, double-blind, two-period, cross-over, glucose clamp trial. The subjects were given an individual need–derived dose of prandial insulin lispro or aspart immediately before a standard mixed meal.

RESULTS — With respect to blood glucose excursions from time 0 to 6 h ($Exc_{glu(0-6\ h)}$) and from time 0 to 4 h ($Exc_{glu(0-4\ h)}$), the pharmacodynamic effect of insulin aspart and insulin lispro can be declared equivalent. This was supported by comparison with maximum postprandial blood glucose excursions ($C_{max(glu)}$) (estimated ratio aspart/lispro ANOVA [90% CI]: 0.95 [0.80–1.13], 0.97 [0.82–1.17], and 1.01 [0.95–1.07] for $Exc_{glu(0-6\ h)}$, $Exc_{glu(0-4\ h)}$, and $C_{max(glu)}$, respectively). For pharmacokinetic end points (maximum postprandial insulin excursions and area under the curve for insulin from time 0 to 6 h and from time 0 to 4 h), equivalence was indicated. No difference concerning absorption or elimination for time to maximal insulin concentration, time to half-maximum insulin concentration, and time to decrease to 50% of maximum insulin concentration was observed.

CONCLUSIONS — These data suggest that in type 1 diabetic patients, both insulin analogs are equally effective for control of postprandial blood glucose excursions.

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In accordance with the results of the Diabetes Control and Complication Trial, near-normoglycemic blood glucose levels prevent the onset or delay the progression of long-term complications in type 1 diabetes (1). To mimic the physiological insulin secretion profile, intensified insulin therapy with unmodified human soluble insulin is performed as standard treatment regimen by a majority of patients (2,3). However, postprandial blood glucose peaks and excursions are not comparable with nondiabetic subjects. Absorption of unmodified insulin from the injection site is a complex process affected by only partially changeable factors, such as anatomic area, blood flow, injection volume, concentration of insulin, and possible local degradation process (4–6). Therefore, considerable attention has been devoted to the development of insulin molecules with accelerated absorption kinetics (7–9). This more physiological profile of these short-acting insulin analogs leads to reduced prandial glucose excursions (10–13). In well-controlled type 1 diabetic patients, postprandial administration of insulin aspart and insulin lispro has shown to be at least as effective as mealtime application of soluble human insulin (14,15). These pharmacokinetic properties should allow greater flexibility, enable patients to adjust their insulin dosage more precisely according to the amount of ingested carbohydrates, and might improve quality of life for type 1 diabetic patients (16,17).

Though it is well documented that each analog has advantageous postprandial glucose control compared with human soluble insulin, until now a complete direct comparison of pharmacokinetic and pharmacodynamic properties of both analogs in a setting close to the daily life of diabetic patients has not been performed. The aim of this study was to investigate prandial glycemia after the subcutaneous injection of insulin aspart or insulin lispro after a standard meal and to determine whether one of the two analogs might have favorable effects on postprandial blood glucose control.

RESEARCH DESIGN AND METHODS

— The study was approved by the local ethical committee of the Karl-Franzens University Graz and performed in accordance with the principles expressed in the Declaration of Hel-

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Abbreviations: AUC_{ins}, area under the curve for insulin; C_{max}, maximum baseline-corrected concentration; Exc_{glu}, blood glucose excursion; $t_{50\%decrease(ins)}$, time to decrease to 50% of maximum insulin concentration; $t_{50\%\ of\ peak(ins)}$, time to half-maximum insulin concentration; $t_{peak(ins)}$, time to maximal insulin concentration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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sinki (18). All subjects gave written informed consent before entry into the trial.

Subjects

The patients recruited were adult men and women according to World Health Organization criteria (19). Their duration of diabetes was ≥24 months, and all patients were treated with intensified insulin therapy, including meal-related human soluble insulin and NPH insulin twice daily ($n = 19$) or continuous subcutaneous insulin therapy ($n = 5$), for at least 3 months. None of the patients had active proliferative retinopathy, clinical significant nephropathy or neuropathy, recurrent severe hypoglycemia, or required ≥ 1.4 units $\cdot kg^{-1} \cdot day^{-1}$ insulin. We randomized 8 women and 16 men with a mean (±SD) age of 36 ± 8 years (range 20–47), BMI 24.3 ± 2.6 kg/m^2 (18.3–29.4), diabetes duration 17 ± 11 years (3–44), and HbA_{1c} 7.9 ± 0.8% (6.6–9.8). Their mean daily total insulin dose was 49.1 ± 13.9 IU (27–83) and was derived from a bolus need of 24.7 ± 11.3 IU (9–47) and basal insulin requirements of 24.4 ± 7.6 IU (12–36).

Study design

The study was conducted as a single-center, randomized, double-blind, two-period, cross-over, clamp trial. The subjects fulfilling all inclusion criteria after the screening visit were assigned a patient number in ascending order on the first study day and randomly allocated to receive either insulin aspart or insulin lispro in a predetermined sequence. The test medication was injected subcutaneously in a skin fold in the left anterior abdominal wall by a study nurse; hence, all investigators and patients were blinded with regard to the respective type of insulin treatment. Patients were studied on two different occasions separated by 4–14 days. On study days, patients were admitted in a fasting state to the clinical research center at 7:30 A.M. Patients on intensified insulin therapy with multiple injections omitted their usual morning NPH insulin injection to avoid any influence of variable absorption kinetics of long-acting insulin (20). Patients on continuous subcutaneous insulin infusion stopped their running basal rate at arrival. Variable insulin rates were infused to cover each patient's basal insulin requirements and to achieve a target blood glucose level of 6.7 mmol/l (range 5.6–7.8) (21). Adjustment of the insulin infusion rate was allowed until 11:00 A.M. (−60 min) and was kept constant thereafter throughout the experiment. Experiments were only performed if plasma glucose values remained stable between 5.6 and 7.8 mmol/l during the 60-min period before test meal (idealized basal insulin requirements). At 12:00 A.M. (time 0), the patients received a single dose of insulin aspart (100 units/ml Novorapid; Novo Nordisk, Bagsvaerd, Denmark) or insulin lispro (100 units/ml Humalog; Eli Lilly, Indianapolis, IN) in random order. The corresponding substance was administered at the next visit. A standardized meal was served (595 kcal; 50% carbohydrates, 15% proteins, and 35% fat) and ingested without any time delay. This meal was identical for all patients on all study days. The dose of insulin to cover the standardized meal was kept identical for both visits (mean 7.1 ± 1.3 IU, range 5–9) and was derived from the individual need in accordance to the patient's log book. For evaluation of blood glucose and serum insulin, blood samples were drawn at 15-min intervals, from −45 min to time of insulin injection (0 min), every 10 min until 120 min, and thereafter every 20 min until the end of the experiment. To avoid hypoglycemia in the postprandial phase (if glucose level fell below 3.3 mmol/l), glucose was infused intravenously. Between experiments, the patients continued their usual intensified insulin therapy.

Analytical methods

HbA_{1c} was analyzed using the Unimate HbA1c (Roche Diagnostics; reference interval 4.5–5.7%). Plasma glucose was measured in duplicate using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). The measured serum human insulin, insulin aspart, and insulin lispro concentrations were corrected for endogenous insulin, which was estimated based on the measured C-peptide concentration in the serum (22) using Dako C-peptide ELISA (Dako Diagnostics, Ely, Cambridgeshire, U.K.). Total serum human insulin, insulin aspart, and lispro insulin were measured with Pharmacia Insulin RIA 100 (Pharmacia Diagnostics AB, Uppsala, Sweden). The measured serum insulin lispro was corrected for nonlinearity using a similar method to that previously described by Andersen et al. (23) for insulin aspart. The difference between the lispro and aspart correction was due to different constant values in the nonlinearity correction formula for the two analogs: true concentration = $S \times X/(T - X)$, where X is the measured analog concentation (in picomoles per liter) and S and T are constants (S = 2,533 and T = 1945 for lispro; S = 1,503 and T = 1,398 for aspart).

Statistical methods

Statistical analysis was based on the intention-to-treat population. The trial was dimensioned as an equivalence trial based on the primary efficacy end point, blood glucose excursion from time 0 to 6 h ($Exc_{glu(0-6\ h)}$) relative to the standardized meal. A sample size of 24 subjects was calculated on the basis of a paired *t* test using the Scuirmann's Two One-sided Test Procedure, assuming that the true difference between the treatments is zero, and was estimated to give a power of 80%. Based on recently published guidelines (24), equivalence was established if the 90% CI of the ratio of the mean differences was within 80–125%, corresponding to ±0.22 on the log scale. $Exc_{glu(0-6\ h)}$ and $Exc_{glu(0-4\ h)}$ were calculated as the total area between the glucose concentration profile and the horizontal line defined by the average of the baseline values at −45, −30, and −15 min and logarithmically transformed and subjected to ANOVA, including treatment, visit, and sequence as fixed effects and subject as random effect. As a secondary end point, the maximum baseline-corrected blood glucose concentration ($C_{max(glu)}$) was assessed in the same model as stated above. Furthermore, the insulin concentration profiles ($C_{max(ins)}$) and area under the curve for insulin from time 0 to 4 h ($AUC_{ins(0-4\ h)}$), $AUC_{ins(0-6\ h)}$, and $AUC_{ins(4-6\ h)}$ were obtained as secondary end points. The AUCs were calculated by a trapezoidal method. Time to maximal insulin concentration ($t_{peak(ins)}$), time to half-maximum insulin concentration ($t_{50\%\ of\ peak(ins)}$), and time to decrease to 50% of maximum insulin concentration ($t_{50\%decrease(ins)}$) were performed nonparametrically using a Wilcoxon's signed-rank test on paired differences. Statistical analyses were made using SAS for UNIX, version 6.12 (SAS Institute, Cary, NC). Data are generally presented as means ± SE, unless otherwise indicated.

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Table 1—*Blood glucose excursions from 0 to 6 h after a standard meal*

$Exc_{glu(0–6\ h)}$ (mmol · l^{-1} · min)	Aspart	Lispro
N	24	24
Arithmetic mean	1,093.1	1,221.7
SE	104.5	143.9
Geometric mean	6.9	6.9
Coefficient of variation (%)	46.8	57.7
Minimum to maximum	405.0–2,233.3	412.3–2,486.4

RESULTS — A total of 27 patients were screened for the trial. Three subjects were screening failures due to nonfulfilment of inclusion/exclusion criteria. All 24 subjects randomized and exposed to trial products completed the trial. Doses of human insulin infusion rates for obtaining the idealized basal insulin requirements were comparable for both treatment sequences. In all experiments, the target blood glucose level of 6.7 mmol/l (range 5.6–7.8) was achieved during the 60-min period before the insulin injection.

Pharmacodynamics

The results for the primary efficacy end point ($Exc_{glu(0–6\ h)}$) are summarized in Table 1. The 90% CI of the ratio of insulin aspart/insulin lispro was completely contained within the 80–125% interval (ANOVA [90% CI]: 0.95 [0.80–1.13]). Plasma glucose profiles for both treatments were congruent throughout the whole experiment (Fig. 1*A*). The analysis of $Exc_{glu(0–4\ h)}$ (insulin aspart 727.6 ± 66.5 mol · l^{-1} · min and insulin lispro 780.6 ± 86.6 mmol · l^{-1} · min; ANOVA [90% CI]: 0.97 [0.82–1.17]) and $C_{max(glu)}$ (insulin aspart 11.9 ± 0.4 mmol/l and insulin lispro 11.9 ± 0.5 mmol/l) in both insulin groups (Fig. 1*B*) supports the declaration of equivalence of the pharmacodynamic effects of the analogs (ANOVA [90% CI]: 1.01 [0.95–1.07]).

Pharmacokinetics

In Fig. 2*A*, serum insulin levels are shown. Average serum insulin before injection of the test medication was 89 pmol/l and stable through the whole run-in period, indicating stable conditions before the test meal. Based on the serum insulin profiles, equivalence could be declared for pharmacodynamic parameters ($C_{max(ins)}$, $AUC_{ins(0–6\ h)}$, and $AUC_{ins(0–4\ h)}$), in which 90% CIs were within the specified 80–125% range (Table 2). Insulin aspart reached $t_{50\%\ of\ peak(ins)}$ at 19.6 ± 1.7 min and insulin lispro at 16.7 ± 1.8 min (P = 0.29), and $t_{peak(ins)}$ was reached at 43.8 ± 3.9 min with insulin aspart and at 46.7 ± 4.7 min with insulin lispro (P = 0.66). Furthermore, no statistical difference between the two treatment groups for $t_{50\%decrease(ins)}$ was observed (insulin aspart 113.1 ± 9.3 min and insulin lispro 115.7 ± 9.7 min, P = 0.67) (Fig. 2*B*).

Hypoglycemia

To avoid hypoglycemia (plasma glucose <3.3 mmol/l) during the postprandial phase, intravenous administration of glucose was necessary in seven experiments in seven patients (two insulin aspart and five insulin lispro patients, P = 0.41, two-tailed Fisher's exact test). The mean time of intervention was 257 min (range 145–350) after the start of the meal.

Safety

No adverse events were reported related to the study medications.

CONCLUSIONS — In our complete head-to-head comparison of the two available short-acting insulin analogs, insulin aspart and insulin lispro, equivalence for the pharmacodynamic could be declared based on the intention-to-treat analysis. Furthermore, for all major

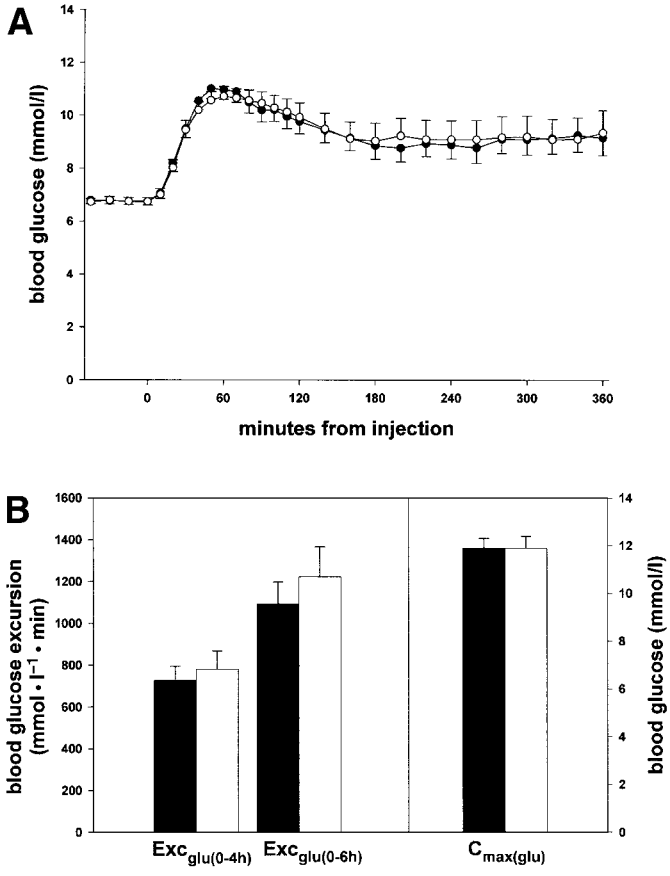

Figure 1—A: *Blood glucose concentrations in 24 patients with type 1 diabetes after injection of insulin aspart (●) and insulin lispro (○) immediately before a standardized meal (time 0). The concentrations are expressed as means ± SE.* B: *Blood glucose excursions from $Exc_{glu(0–4\ h)}$, $Exc_{glu(0–6\ h)}$, and $C_{max(glu)}$ after subcutaneous injection of insulin aspart (■) and insulin lispro (□) immediately before a standardized meal in 24 type 1 diabetic patients. The values are means ± SE.*

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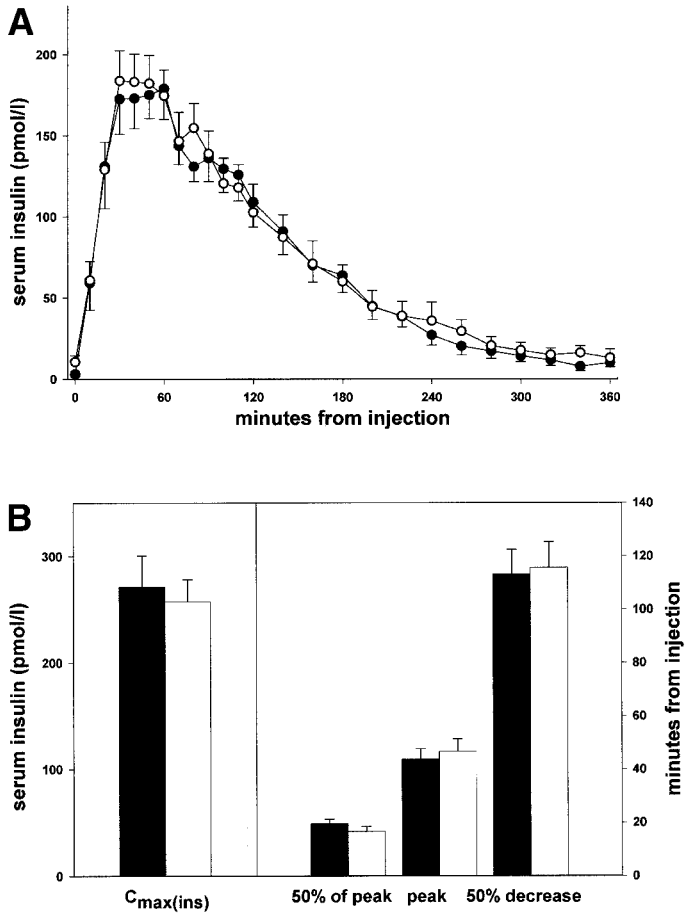

Figure 2—A: *Plasma concentrations of baseline-corrected serum insulin in 24 patients with type 1 diabetes after single subcutaneous injection of insulin aspart (●) and insulin lispro (○) immediately before a standardized meal (time 0). The values are means ± SE.* B: *Time from steady-state conditions to 50% of peak concentrations, peak concentrations, and 50% decrease from peak concentration after subcutaneous injection of insulin aspart (■) and insulin lispro (□). The values are means ± SE.*

pharmacokinetic parameters ($C_{max(ins)}$, $AUC_{ins(0-6\ h)}$, $AUC_{ins(0-4\ h)}$, $t_{peak(ins)}$, $t_{50\%\ of\ peak(ins)}$, and $t_{50\%decrease(ins)}$), equivalent properties were demonstrated.

In the trial, we tried to control for those factors influencing both postprandial glucose excursions and insulin absorption. A clamp procedure with a variable insulin infusion was used to cover patients' basal insulin requirements and to achieve a comparable isoglycemic preprandial blood glucose level. In addition, time of injection of test substance was at 12:00 A.M., which levels possible carry-over effects of the basal insulin injected at bedtime. Our findings were confirmed by an analysis of the subgroups of pump users versus patients on multiple injections. The recently proposed small differences (25) in absorption kinetics between the two short-acting insulin analogs could not be confirmed. As discussed by the authors of that investigation (25), various factors may have an impact on absorbtion kinetics. The larger number of subjects studied in our trial may have eliminated further source of variation. Moreover, the data presented here include a complete pharmacodynamic comparison ($Exc_{glu(0-6\ h)}$, $Exc_{glu(0-4\ h)}$, and $C_{max(glu)}$), which is the most relevant patient-related outcome. Not surprisingly, based on the identical pharmacokinetic profile, glucose excursions and peak glucose values were similar.

For the last 2 h, the blood glucose observed remained at a higher level of ~2 mmol/l above preprandial level. The most likely explanation for this finding is reduced physical activity on study days. Furthermore, all patients were routinely taking NPH insulin twice daily. The peak action of NPH insulin injected in the morning may, at lunchtime, partially contribute to prandial insulin need in daily life but was missing on study day. Therefore, the dose derived from the patient's logbook might have been too low to reduce blood glucose excursion to preprandial levels. However, this finding was similar in both groups and does not contribute to the main finding of this study. In addition, frequency of postprandial hypoglycemia was not statistically different ($P = 0.41$) in both groups and low compared with other studies (14).

For pharmacokinetic assessment, we did not use a methodology to separate free insulin from insulin bound to antibodies. The cross-over design used in the study should exclude a misinterpretation of the data. Moreover, all patients were naive to insulin aspart or insulin lispro and the baseline antibody titer measured was low.

The principle of short-acting insulin analogs was introduced to achieve insulin profiles in intensified insulin therapy as close to physiological levels as possible. Reduced tendency for self-association of insulin lispro and insulin aspart leads to faster absorption and higher peak insulin levels in both type 1 and type 2 diabetic patients. For long-term parameters, such as HbA_{1c} and frequency of hypoglycemia, only minor changes were observed compared with regular insulin (12,13,26–28). The data presented in this publication clearly indicate identical pharmacodynamic and pharmacokinetic properties; therefore, no clinical differ-

Table 2—*Pharmacokinetics based on 6-h serum insulin profiles*

	Aspart	Lispro	ANOVA (ratio [90% CI])
C_{max} (pmol/l)	271.4 ± 29.3	257.6 ± 20.5	1.01 [0.95–1.11]
$AUC_{(0-4\ h)}$ (pmol · l^{-1} · min)	23,653.6 ± 2269.9	23,411.1 ± 1896.8	0.99 [0.90–1.08]
$AUC_{(0-6\ h)}$ (pmol · l^{-1} · min)	24,074.3 ± 2321.8	24,537.2 ± 2119.3	0.97 [0.88–1.06]
$AUC_{(4-6\ h)}$ (pmol · l^{-1} · min)	420.7 ± 113.4	1,126 ± 385.2	0.62 [0.30–1.27]

Data are means ± SE.

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ence can be expected when comparing these two analogs. This finding is consistent with a recent clinical publication by Bode et al. (26).

In conclusion, based on a complete head-to-head comparison, both insulin analogs are equally effective for control of postprandial blood glucose excursions.

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