Pharmacokinetics, Prandial Glucose Control, and Safety of Insulin Glulisine in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE — The aim of this study was to investigate the pharmacokinetics, postprandial blood glucose excursions, and safety of insulin glulisine as compared with regular human insulin (RHI), both administered immediately before meals in pediatric patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A total of 10 children (aged 5–11 years) and 10 adolescents (aged 12–17 years) were enrolled in a randomized, single-center, single-dose, double-blind, cross-over study. The blood glucose of fasting patients was stabilized with intravenous insulin, following which patients received 0.15 IU/kg of subcutaneously injected insulin glulisine or RHI 2 min before a weight-adjusted standardized liquid meal.

RESULTS — For insulin glulisine versus RHI, maximum insulin concentrations (58 vs. 33 μIU/ml, $P < 0.05$) and initial insulin concentrations (insulin [area under the curve] AUC_{0-2h} 5,232 vs. 2,994 μIU $\cdot$ min^{-1} $\cdot$ ml^{-1}, $P < 0.05$; data are geometric means) were higher after insulin glulisine than RHI. Both time to maximum insulin concentration (54 vs. 66 min) and mean residence time (88 vs. 137 min, $P < 0.05$) were shorter with insulin glulisine versus RHI. Postprandial glucose excursions after insulin glulisine were lower than after RHI (glucose AUC_{0-6h} 641 vs. 801 mg $\cdot$ h^{-1} $\cdot$ dl^{-1}, $P < 0.05$). The pharmacokinetic profile for insulin glulisine was similar for children and adolescents, whereas the pharmacokinetic profile for RHI demonstrated a 64% higher concentration in adolescents. Insulin glulisine was safe and well tolerated.

CONCLUSIONS — The rapid-acting properties of insulin glulisine that have been previously demonstrated in adults are also observed in children and adolescents with type 1 diabetes. Further, these initial data indicate that insulin glulisine is safe and well tolerated in this patient population.

Diabetes Care 28:2100–2105, 2005

T he goal of basal-bolus insulin therapy in type 1 diabetes is to achieve near to normal glycemic control and reduce the risk of long-term clinical complications (1). Children and adolescents sometimes encounter difficulties in adjusting their daily activities to fixed intervals between insulin administration and meals, particularly with regular human insulin (RHI), which requires administration 30–45 min before mealtime (2). The use of rapid-acting insulin analogs instead of RHI for prandial glycemic control is becoming increasingly accepted, since these insulins can be given much closer to mealtime (2–4). Thus, rapid-acting insulin analogs might offer advantages, particularly for very young children in whom the actual carbohydrate intake is often difficult to predict (5). It remains to be shown, however, whether the rapid-acting properties of these analogs are preserved in children.

Insulin glulisine ([LysB3, GluB29]-insulin) is a recombinant insulin analog designed to provide the same total glucodynamic effect as RHI after subcutaneous administration but with a faster onset and shorter duration of action (6), which has been demonstrated in adults (7–9). The altered absorption of insulin glulisine results from the replacement of asparagine with lysine at position 3 and of lysine by glutamic acid at position 29 on the B-chain of the human insulin molecule. These substitutions reduce the formation of oligomers and favor stable monomers, enhancing absorption from the subcutaneous tissue (10,11).

The objective of this study was to investigate the pharmacokinetic properties of insulin glulisine in comparison to RHI to confirm the rapid-acting properties of this novel insulin analog in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This study compared the pharmacokinetic postprandial glucose excursions and safety profile of insulin glulisine (supplied at 1 ml equimolar to 100 units human insulin; Aventis Pharma, Frankfurt, Germany) and RHI (Aventis Pharma) in children and adolescents with type 1 diabetes. In this single-center, single-dose, double-blind, two-way cross-over trial, pediatric patients

received subcutaneous injections of 0.15 IU/kg insulin glulisine or RHI 2 min before a standardized meal. Study days were separated by at least 3 and no more than 14 days. The study was approved by an independent ethics committee, and assent and written informed consent were obtained from either the patients' representative or from the patients themselves when they were able to understand the informed consent. The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and its amendments.

The patients' usual insulin treatment was suspended from the evening before the study day until the end of the study day. Patients also fasted from their evening meal on the day before the study visits until a standardized liquid meal was administered on the study day itself. A variable intravenous infusion of RHI was used to maintain patients' blood glucose levels at 100–160 mg/dl (5.6–8.9 mmol/l) before the experiment; this variable infusion was discontinued 20 min before subcutaneous injection of insulin glulisine or RHI, respectively.

After two consecutive blood glucose measurements taken 30 min apart were within the target range, a subcutaneous injection of either insulin at a dose of 0.15 IU/kg was given in the periumbilical area of the abdomen.

Two minutes after the administration of the study medication, a standardized liquid meal (composition for 8 fl oz: 240 kcal, 4 g fat, 41 g total carbohydrate, and 10 g protein) (Boost; Novartis Medical Nutrition, München, Germany) was given to compensate for the glucose-lowering effect of the added exogenous insulin and to prevent hypoglycemic events. The amount of Boost given was adjusted according to patients' weight as follows: patients who weighed 20–30 kg received 197 ml Boost, those weighing 30–40 kg received 296 ml, patients weighing 40–50 kg were given 394 ml, and those patients >50 kg received 493 ml. Patients remained fasted until 6 h after the standardized liquid meal, at which point a regular meal was given and patients resumed their usual therapy. If blood glucose fell below 90 mg/dl (50 mmol/l), 10 g carbohydrate was administered orally. Samples for pharmacokinetic and blood glucose measurements were collected for 6 h after insulin injection in all patients.

Assessments and data analysis
Radioimmunoassays were used for the determination of human insulin and insulin glulisine concentrations. Unbound, free insulin concentrations were measured after polyethylene glycol precipitation to separate the bound from the free-insulin fraction. Insulin glulisine concentrations were quantified with a radioimmunoassay specific for insulin glulisine at a limit of quantification of 5 μIU/ml with a working range of 5–200 μIU/ml (sanofi-aventis, data on file). The limit of quantification of human insulin was 4.3 μIU/ml with a working range of 4.3–138 μIU/ml.

Blood glucose concentrations were measured by the glucose oxidase method with a Glucometer Elite (Bayer, Leverkusen, Germany) at the bedside.
Pharmacokinetics. The serum insulin profile was characterized by the area under the insulin concentration–time curve at the following times after injection: 1 h (INS $AUC_{0–1h}$), 2 h (INS $AUC_{0–2h}$), 4 h (INS $AUC_{0–4h}$), and 6 h (INS $AUC_{0–6h}$). In addition, maximum insulin concentration (C_{max}), the time to maximum insulin concentration (t_{max}), and mean residence time (MRT) were also calculated.
Postprandial glucose excursions. Postprandial blood glucose was assessed as the area under the baseline subtracted blood glucose concentration–time curve at the following times after injection: 1 h (BG $AUC_{0–1h}$), 2 h (BG $AUC_{0–2h}$), 4 h (BG $AUC_{0–4h}$), and 6 h (BG $AUC_{0–6h}$), along with the maximum blood glucose concentration (BG_{max}), maximum blood glucose excursion from baseline (ΔBG_{max}), and minimum blood glucose concentration (BG_{min}). A single baseline blood glucose concentration was calculated as the median glucose concentration from the three measurements (-60, -30, and 0 min) taken before study medication administration.
Safety data. Hematology, clinical chemistry, human insulin antibodies at baseline, urinalysis, physical examination, blood pressure, pulse rate, core body temperature, injection site reactions, and adverse events were collected for the safety analysis.

Statistical analysis
**Pharmacokinetics.** The conventional bioequivalence range of 80–125% for pharmacokinetic variables was used as a guideline to judge the equivalence of the two insulin treatments. ANOVA for INS AUCs, MRT, and C_{max}, with adjustments for treatment, period, sequence and subject-within-sequence effects, were performed using natural log–transformed values to compare treatments within age-groups. ANOVAs with adjustments for age-group, period, sequence, and subject-within-sequence effects were also performed to compare age-groups within treatment. Point estimates and 95% CIs were calculated for the treatment ratios and for the age-group ratios per treatment. Nonparametric analyses were used to analyze t_{max}, while 95% nonparametric CIs for the respective median treatment and age-group differences were calculated. No adjustment of alpha levels for multiple testing or CIs was made.
Postprandial blood glucose concentrations and excursions. Blood glucose parameters (i.e., BG AUCs, BG_{max}, ΔBG_{max}, and BG_{min}) were analyzed using ANOVAs. The ANOVAs (with adjustments for treatment, period, sequence, and subject-within-sequence effects included) were performed by age, class, and point estimates, and 95% CIs were calculated for the treatment ratios. The time parameters were analyzed by nonparametric analyses, and 95% nonparametric CIs for the respective median treatment and age-group differences were calculated.

RESULTS

Study patients and conduct
Twenty pediatric patients (9 male and 11 female) with type 1 diabetes, disease duration 1–15 years, $HbA_{1c} \leq 11\%$, and BMI 16.4–26.3 kg/m^2 were enrolled. Patients were stratified according to age into two groups of 10 patients each: children (aged 5–11 years, mean 10.1) and adolescents (aged 12–17 years, 14.7). The mean weight for children was 40.0 kg (range 26.0–50.0), and the mean weight for adolescents was 64.2 kg (51.0–82.5). Heights of the children ranged from 125.0 to 154.0 cm (mean 142.6), while the range of heights for the adolescent patient group was 158.0–180.0 cm (168.7). The study test dose was 5.9 ± 2.2 IU for children and 9.7 ± 3.0 IU for adolescents (mean ± 2 SD). Mean basal blood glucose levels were similar in patients immediately before receiving either insulin glulisine (children 130 mg/dl, adolescents 135 mg/dl) or RHI (children 133 mg/dl,
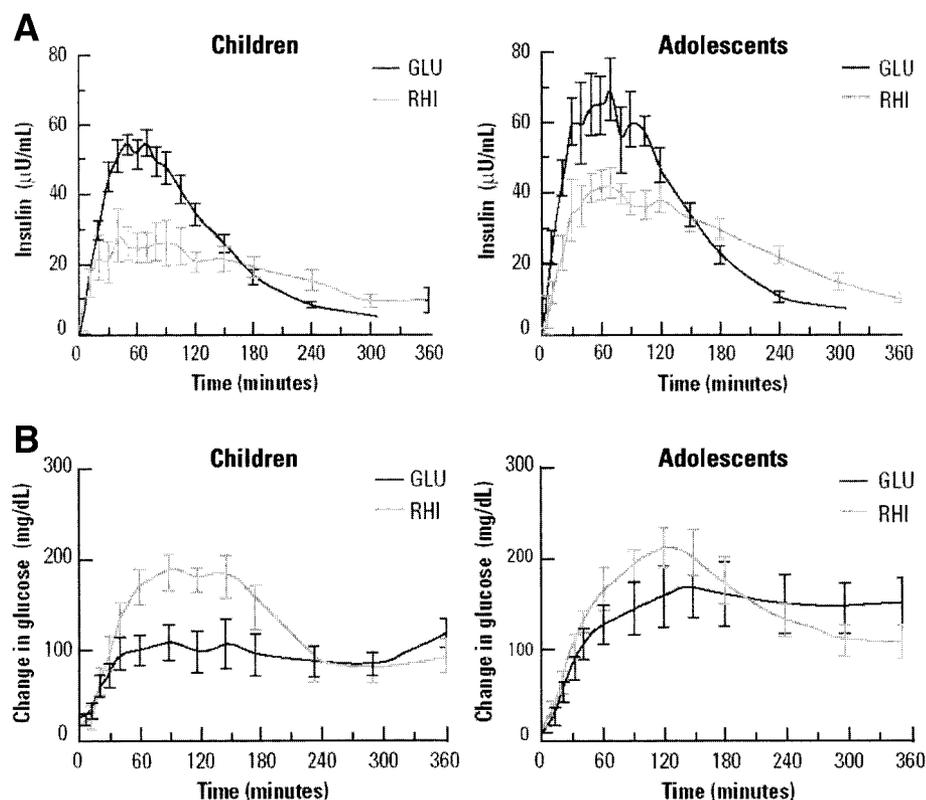
Figure 1—*Serum insulin (A) and postprandial blood glucose (B) after subcutaneous injection of 0.15 IU/kg insulin glulisine and regular human insulin in children and adolescents.*

insulin concentration, as assessed by INS AUC_{0-1h} and INS AUC_{0-2h}, was higher for insulin glulisine than for RHI ($P < 0.05$), while the overall concentrations (INS AUC_{0-6h}) were comparable. The MRT for insulin glulisine was distinctly shorter at 88 min compared with 137 min for RHI ($P < 0.05$), indicating the shorter residence of insulin glulisine in the systemic circulation.

Children and adolescents presented almost equal pharmacokinetic profiles of insulin glulisine, displayed by point estimates close to 100% (Table 1). This was in contrast to the results for RHI, where the ratio of geometric means for INS AUC_{0-4h} comparing adolescents (geometric mean: 7,367 $\mu IU \cdot min^{-1} \cdot ml^{-1}$) with children (4,530 $\mu IU \cdot min^{-1} \cdot ml^{-1}$) was 163% ($P < 0.05$), compared with 112% for insulin glulisine (children 7,193 $\mu IU \cdot min^{-1} \cdot ml^{-1}$, adolescents 8,081 $\mu IU \cdot min^{-1} \cdot ml^{-1}$). Similarly, the ratio of geometric means for C_{max} in adolescents compared with children was ~77% higher with RHI ($P < 0.05$) than with insulin glulisine. There were no significant differences in t_{max} and MRT between age-groups for either study insulin.

adolescents 123 mg/dl). In addition, the C-peptide data taken 60 min after the start of the meal showed that concentrations of insulin in all patients were <0.2 nmol/l (range <0.03–0.2), confirming severe type 1 diabetes. One subject was excluded from pharmacokinetic analysis of RHI due to an inconsistent concentration–time profile.

Pharmacokinetics

The C_{max} after insulin glulisine compared with RHI was higher by 71% ($P < 0.05$) (Fig. 1A; Table 1). Likewise, the initial

Postprandial glucose excursions

BG AUCs, BG_{max}, and ΔBG_{max} were significantly lower after insulin glulisine versus RHI in the pediatric patients for the entire postprandial monitoring period (all $P < 0.05$) (Fig. 1B; Table 2). This trend was maintained even when the results

Table 1—*Pharmacokinetic results for all patients*

| | Geometric mean | | | | | | Point estimate (95% confidence limits)* | | |
| | All | | Children | | Adolescents | | All | Adolescents/children | |
	Glu	RHI	Glu	RHI	Glu	RHI	Glu/RHI	Glu	RHI
n	20	19	10	10	10	9	19	10	9
INS $AUC_{(0-1h)}$ ($\mu IU \cdot min^{-1} \cdot ml^{-1}$)	2,287	1,246	2,170	1,023	2,410	1,552	176% (127, 244)	111% (70, 175)	152% (89, 258)
INS $AUC_{(0-2h)}$ ($\mu IU \cdot min^{-1} \cdot ml^{-1}$)	5,232	2,994	4,948	2,383	5,534	3,860	169% (127, 224)	112% (72, 174)	162% (105, 250)
INS $AUC_{(0-4h)}$ ($\mu IU \cdot min^{-1} \cdot ml^{-1}$)	7,624	5,703	7,193	4,530	8,081	7,367	130% (99, 170)	112% (72, 175)	163% (111, 238)
INS $AUC_{(0-6h)}$ ($\mu IU \cdot min^{-1} \cdot ml^{-1}$)	8,361	7,052	7,934	5,581	8,811	9,145	116% (90, 150)	111% (73, 169)	164% (114, 236)
C_{max} ($\mu IU/ml$)	58	33	55	25	61	44	171% (127, 229)	112% (73, 172)	177% (112, 281)
t_{max} (min)	54†	66†	55†	59†	52	76†	−8 min (−24, 7)‡	−2 min (−9, 11)	9 min (−24, 49)
MRT (min)	88	137	87	132	90	144	64% (59, 70)	103% (88, 121)	110% (92, 130)

*Point estimates (95% confidence limits) for the ratio of treatment means. †Median; ‡point estimates (95% confidence limits) for the respective median differences from nonparametric data analysis. Glu, glulisine.

Table 2—*Postprandial glucose for all patients*

| | Arithmetic mean | | | | | | Point estimate (95% confidence limits)* | | |
| | All | | Children | | Adolescents | | All | Adolescents/children | |
	Glu	RHI	Glu	RHI	Glu	RHI	Glu/RHI	Glu	RHI
n	20	20	10	10	10	10	20	10	10
BG AUC$_{(0–1h)}$ (mg $\cdot$ h^{-1} $\cdot$ dl^{-1})	57	79	50	75	65	82	73% (59, 90)	131% (69, 287)	108% (70, 171)
BG AUC$_{(0–2h)}$ (mg $\cdot$ h^{-1} $\cdot$ dl^{-1})	179	263	149	258	208	267	68% (56, 82)	140% (82, 269)	103% (74, 144)
BG AUC$_{(0–4h)}$ (mg $\cdot$ h^{-1} $\cdot$ dl^{-1})	419	627	320	590	518	664	67% (55, 80)	162% (87, 395)	113% (81, 159)
BG AUC$_{(0–6h)}$ (mg $\cdot$ h^{-1} $\cdot$ dl^{-1})	641	801	492	729	790	872	80% (67, 95)	161% (88, 369)	120% (82, 179)
BG$_{max}$ (mg/dl)	298	352	273	349	324	355	85% (77, 93)	119% (92, 155)	102% (84, 124)
ΔBG$_{max}$ (mg/dl)	166	224	142	216	189	232	74% (64, 86)	133% (84, 226)	107% (81, 143)
BG$_{min}$ (mg/dl)	211	193	180	179	242	207	109% (93, 128)	135% (95, 199)	115% (83, 162)

Data are baseline corrected. *Point estimates (95% confidence limits) for the ratio of treatment means according to Fieller's Theorem. Glu, glulisine.

from children and adolescents were analyzed separately. After insulin glulisine, but not after RHI injection, blood glucose tended to increase toward the end of the 6-h monitoring period.

Safety

A total of 19 mild adverse events were reported in nine patients, of which one (urticaria) was reported to be possibly related to study medication (RHI). There were no events of severe hypoglycemia or clinically relevant abnormalities in the physical examinations or in the laboratory variables. There were no injection site reactions.

CONCLUSIONS — This study demonstrates that higher initial concentrations of insulin glulisine were seen in pediatric patients with type 1 diabetes than with RHI, with a clinically meaningful difference in the INS AUC in the first 2 h between the two treatment groups. Likewise, the maximum serum insulin concentration for insulin glulisine was 71% higher compared with RHI. In contrast to the initial concentrations, the total insulin concentrations over the first 6 h after injection were similar for insulin glulisine and RHI in the pediatric patients investigated. The MRT in this study was significantly lower for insulin glulisine than RHI, indicating a shorter residence in the systemic circulation. Hence, in this study investigating pediatric patients with type 1 diabetes, pharmacokinetic properties, which are characteristic of rapid-acting insulin analogs, are demonstrated with the use of insulin glulisine (12,13).

The pharmacokinetic results are reflected in postprandial glucose profiles, as demonstrated by lower glucose excursions with insulin glulisine compared with RHI. As there were no differences in basal blood glucose levels between the two treatment groups, these results are due to the drug alone and not due to other factors such as glucose fluctuations due to hormonal adaptations and glucose absorption effects after a meal. Notably, blood glucose levels generally increased toward the end of the 6-h monitoring period in patients treated with insulin glulisine, reflecting the absence of a basal insulin. In contrast, the values following RHI administration remained unchanged in this period, reflecting its longer duration of action. A very similar pharmacodynamic picture has been reported for insulin aspart (14), and a similar disparity between blood glucose levels beyond 4 h postdosing has also been seen in a study of insulin glulisine in adults (15). These results indicate that when using rapid-acting insulin analogs, an adjustment of basal insulin may be required, compared with RHI, to obtain optimum glycemic control in the late postprandial period. However, in a separate study in adult patients with type 1 diabetes using insulin glulisine, the basal insulin requirement did not increase (16).

The use of a radioimmunoassay that was specific for insulin glulisine allowed insulin glulisine concentrations in the presence of human insulin to be determined precisely. According to the study protocol, patients had to be treated with an intravenous infusion of human insulin before injection of the study medication; hence contamination a priori, in principle at least, could not be excluded. However, contamination with human insulin is lim-ited, with respect to the degree of contamination (human insulin was infused intravenously at a low dose, compared with the insulin glulisine injected subcutaneously) and with respect to the timeframe (human insulin intravenous infusion was stopped 20 min before the subcutaneous injection of the study drug). Therefore, at the time of peak insulin absorption following the subcutaneous injection, almost no residual human insulin would be expected in the intravascular space.

In the study presented here, patients received RHI immediately before meals, although a 15–30 min interval between injection and ingestion is recommended (17). However, it is well known that many patients with diabetes inject regular insulin immediately before or even after the ingestion of food (18). Hence, we decided to include an experiment with RHI injected immediately prior to a meal in the study to compare postprandial blood glucose excursions following an insulin regimen often practiced by patients with diabetes (though not recommended). Although fixed injection–to–meal dosing intervals are not advantageous for patients in everyday life (19,20), they were necessary in the current study where a predefined, fixed time interval between the injection and the meal was a vital component of the study design, as administering insulin glulisine 30–45 min before the meal may have caused hypoglycemia. However, in acknowledgment of the limitations of fixed injection–meal dosing, a subsequent clinical study with glucose control as the primary objective has incorporated a more flexible dosing–meal regimen.

Of particular interest in the current study is the lack of meaningful differences between children and adolescents with regard to pharmacokinetic properties for insulin glulisine. In contrast, for RHI, C_{max} in this study was 77% higher and overall concentrations of insulin were 64% higher for adolescents compared with children. These findings with RHI are in line with a separate study comparing a rapid-acting insulin analog, insulin aspart, with RHI. In this study, for which there is detailed pediatric pharmacokinetic information, Mortensen et al. (14) describe higher C_{max} both for insulin aspart and for RHI in adolescents compared with children. In the study presented here, treatment with RHI resulted in significantly higher insulin concentrations in adolescents compared with children; however, the insulin concentrations in adolescents treated with insulin glulisine were not statistically higher than in children receiving the same treatment. In both studies, there were no discrepancies between adolescents and children in postprandial blood glucose excursions. Therefore, in the study presented here, with the exception of the results for insulin glulisine, results suggest that higher insulin concentrations are observed with comparable postprandial blood glucose profiles in adolescents compared with children. Any differences may be partially due to disparities in residual endogenous insulin secretion between adolescents and children or as a consequence of the size of the Boost meal given, as the adolescents received a larger meal bolus than the children yet received virtually the same amount of insulin per gram of carbohydrate. However, the results are in line with the relatively impaired insulin sensitivity and higher insulin concentrations reported in healthy adolescents (21,22).

Since meal management in children is difficult, therapy given immediately after a meal to balance the actual carbohydrate intake may be of significant advantage. Optimum management of pediatric patients with diabetes should consider postprandial administration of insulin glulisine. This has been demonstrated to be safe and effective in adults but still requires further investigation in pediatric patients (15,23–25).

In conclusion, insulin glulisine was more rapidly absorbed and had a shorter residence in the systemic circulation than RHI in pediatric and adolescent patients with type 1 diabetes. Thus, insulin glulisine displays pharmacokinetic and pharmacodynamic properties in pediatric patients with type 1 diabetes that classify it as a rapid-acting insulin analog in this population.

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