Advantage of Premeal-Injected Insulin Glulisine Compared With Regular Human Insulin in Subjects With Type 1 Diabetes

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OBJECTIVE — Insulin glulisine, a rapid-acting insulin analog, provides prandial insulin replacement. In this study, we compared postprandial blood glucose control after pre- and postmeal insulin glulisine with regular human insulin (RHI).

RESEARCH DESIGN AND METHODS — In a single-dose, randomized, four-way complete cross-over study, subjects received standardized, 15-min meals, covered by subcutaneous injections of either insulin glulisine (immediately premeal or 15 min postmeal; 0.15 unit/kg per injection) or RHI (30 min or immediately premeal; 0.15 unit/kg per injection). Twenty-one patients with type 1 diabetes (mean age 36.4 years; mean BMI 26.0 kg/m^2) were enrolled; 20 patients completed the study. Postprandial baseline-subtracted blood glucose exposure, maximum excursion, maximum and minimum blood glucose concentrations, and time to the maximum excursion and minimum concentration were assessed, along with serum insulin concentrations.

RESULTS — Lower maximum blood glucose excursion (65 vs. 89 mg/dl), total blood glucose exposure within 2 h (279 vs. 334 mg · h/dl, maximum blood glucose concentration (180 vs. 209 mg/dl), and less time to maximum blood glucose excursion (48 vs. 70 min) were seen with immediately premeal insulin glulisine versus immediately premeal RHI. The maximum serum concentration of insulin glulisine was almost double that of RHI (82 vs. 45 μU/ml), achieved in approximately half the time (55 vs. 97 min). Conversely, insulin glulisine (15 min postmeal) versus RHI (immediately premeal) and RHI (30 min premeal) versus insulin glulisine (immediately premeal) resulted in comparable blood glucose control.

CONCLUSIONS — Insulin glulisine renders postprandial glucose disposal closer to physiologic requirements compared with RHI and enables appropriate timing of prandial insulin administration.

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Tight glycemic control is essential in patients who require insulin for the treatment of diabetes, and its benefits have been clearly demonstrated in several prospective clinical trials, including the Diabetes Control and Complications Trial (DCCT), the U.K. Prospective Diabetes Study (UKPDS), and the Stockholm Diabetes Intervention Study (SDIS) (1–3). Regimens involving multiple daily injections of insulin are designed to achieve tight glycemic control by attempting to mimic physiologic insulin secretion. Before the advent of rapid-acting insulin analogs, regular human insulin (RHI) was the best available treatment option to meet postprandial insulin needs. However, RHI demonstrates a delayed onset of activity after subcutaneous administration, resulting in a recommendation that it should be injected 30 min before a meal (4). Adherence to this recommendation can be inconvenient and has resulted in a substantial proportion of patients negligently injecting closer than 30 min to a meal (5,6).

Insulin glulisine ([LysB3, GluB29] insulin) is a new, rapid-acting insulin analog that was developed to provide a more physiologic prandial insulin replacement compared with RHI to facilitate attainment of glycemic control targets (7–9). Insulin glulisine is a recombinant insulin analog that has a faster absorption rate after subcutaneous injection compared with RHI. This is due to the replacement of asparagine with lysine at position 3 and of lysine with glutamic acid at position 29, on the B-chain of the human insulin molecule.

The primary aim of this study was to compare the pharmacodynamic response to insulin glulisine administered immediately before or after standardized meals with the response to RHI administered 30 min or immediately before meals in subjects with type 1 diabetes. In addition, the pharmacokinetics and safety of both insulin preparations were assessed.

RESEARCH DESIGN AND METHODS

— For this study, we recruited 21 male and female patients with type 1 diabetes, aged 18–55 years, with a BMI of 18–32 kg/m^2, HbA_{1c} (A1C) levels <10%, and serum C-peptide levels ≤0.9 ng/ml to participate as subjects in this trial. Subjects were required to have used the same insulin regimen for ≥2 months before enrollment in the study and were excluded if they were using a total insulin dose of ≥1 unit · kg^{-1} · day^{-1}.

This single-dose, open-label, randomized, four-way cross-over study (study 1008) was conducted at a clinical center in Germany. The study conformed to good clinical practice and the ethical principles of the Declaration of Helsinki. All study documentation was reviewed and approved by an independent ethics committee, with written, informed consent given by all subjects before their participation in the study.

The study comprised six trial periods, which included a screening visit, four treatment periods, and a follow-up visit.

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Abbreviations: AUC, area under the curve; MRT, mean residence time; RHI, regular human insulin; RIA, radioimmunoassay.

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

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Table 1—*Pharmacodynamic data for insulin glulisine and RHI*

	Insulin glulisine		RHI		Point estimate (95% CI)*		
	Immediately premeal (A)	15 min postmeal (B)	30 min premeal (C)	Immediately premeal (D)	Insulin glulisine (A)/ RHI (C)	Insulin glulisine (A)/ RHI (D)	Insulin glulisine (B)/ RHI (D)
BG-$AUC_{(0–2h)}$ (mg · h/dl)	279	337	261	334	23 (−9 to 55)	−49 (−81 to −17)	−3 (−34 to 29)
BG-$AUC_{(0–6h)}$ (mg · h/dl)	708	777	715	770	8 (−86 to 102)	−53 (−148 to 41)	−21 (−115 to 73)
ΔBG_{max} (mg/dl)	65	85	64	89	0.3 (−19 to 20)	−24 (−49 to −10)	−4 (−24 to 15)
BG-t_{max} (min)	48†	45†	115†	70†	−43 (−68 to −13)‡	−17 (−40 to 20)‡	−33 (−50 to −17)‡
BG_{max} (mg/dl)	180	208	177	209	3 (−17 to 22)	−29 (−48 to −10)	−0.2 (−19 to 19)
BG_{min} (mg/dl)	72	75	68	65	4 (−7 to 15)	8 (−4 to 19)	10 (−2 to 21)
BG-t_{min} (min)	275†	255†	325†	311†	−33 (−75 to 5)‡	−25 (−70 to 23)‡	−40 (−78 to −3)‡

Values are arithmetic means or †median values. *Point estimates and 95% CIs for the respective mean differences, from parametric data analysis, expressed as percentages. ‡Point estimates and 95% CIs for the respective median differences, from nonparametric data analysis.

The four treatments consisted of *1*) immediately premeal insulin glulisine (−2 to 0 min before a standardized 15-min meal), *2*) postmeal insulin glulisine (15 min postmeal), *3*) premeal RHI (30 min premeal), and *4*) immediately premeal RHI (−2 to 0 min premeal). The postmeal dosing of insulin glulisine was timed from the start of the meal. Subjects were randomly assigned to the treatments using a Latin-square, four-way, cross-over design with reverse replication of sequences (i.e., ADCB, BCDA, CBAD, and DABC).

Subjects attended the clinic on the evening before study treatment days, where they were prepared with venous lines to receive 20% glucose solution or RHI, as appropriate, to maintain blood glucose levels at 120 mg/dl (6.7 mmol/l). Arterialized (heated box at 55°C) venous blood was drawn for blood glucose determinations. The glucose infusion was discontinued on the morning of each treatment period, and the individual RHI infusion rate was adjusted to maintain blood glucose levels of 100–140 mg/dl (5.6–7.8 mmol/l) without intravenous glucose infusion for ~30 min, before a subcutaneous, periumbilical injection of the study medication (0.15 unit/kg body of insulin glulisine or RHI).

The standardized meal included a skinned banana, milk (1.5% fat), orange juice, and rolled oats totaling 618.2 kcal, 99.4 g carbohydrate, 11.9 g lipid, and 26.2 g protein. Meal consumption lasted a minimum of 10 min but no longer than 15 min. After the meal, subjects fasted for 6 h until another meal was served. Blood glucose levels were determined every 10 min until 60 min before administration of study insulin; blood glucose was initially measured every 5 min until 180 min after dosing, then every 10 min until 360 min after dosing. Serum insulin levels were measured at predefined intervals before the administration of study insulin and for up to 6 h afterward.

Pharmacodynamic assessments

Postprandial blood glucose exposure was assessed as the area under the baseline-subtracted blood glucose concentration-time curve, from time 0 to 2 h (BG-$AUC_{0–2h}$) and 6 h (BG-$AUC_{0–6h}$) after injection, along with the maximum glucose excursion from baseline (ΔBG_{max}) and the time to ΔBG_{max} (ΔBG-t_{max}). In addition, the maximum and minimum postprandial blood glucose concentrations (BG_{max} and BG_{min}) and the time to BG_{min} (BG-t_{min}) were determined. The baseline blood glucose concentrations were calculated as the median of three measurements, taken at −40, −35, and −30 min before study medication administration.

Pharmacokinetic assessments

Pharmacokinetics were assessed from serum insulin glulisine and serum RHI concentrations measured using radioimmunoassays (RIAs). The primary variable was the area under the insulin concentration-time curve from 0 to 2 h after injection (INS-$AUC_{0–2h}$). Additional variables assessed were the area under the insulin concentration-time curve from 0 to 6 h after injection (INS-$AUC_{0–6h}$), the maximum insulin concentration (INS-C_{max}), the time to the maximum insulin concentration (INS-t_{max}), and the mean residence time (INS-MRT).

Safety assessments

Adverse events, hematology, clinical chemistry, urinalysis, and physical examination results were recorded during the study and used as assessments of safety. All safety parameters were assessed by the investigator; subjects provided self-reports of adverse events. Physical examinations included measurements of core body temperature, 12-lead electrocardiogram, and vital signs (blood pressure and radial pulse rate).

Bioanalytics

Blood glucose levels were assessed by a glucose oxidase method using a Super GL glucose analyzer (Ruhrtal Labor Technik, Möhnesee-Delecke, Germany). RIAs were used for the determination of serum concentrations of human insulin and insulin glulisine. Unbound, free insulin concentrations were measured after polyethylene glycol precipitation to separate the antibody-bound insulin from the free-insulin fraction. Insulin glulisine concentrations were quantified with an RIA specific for insulin glulisine, at a limit of quantification of 5 μU/ml, with a working range of 5–200 μU/ml (Linco Research, St. Charles, MO). For human insulin, a nonspecific insulin RIA (Linco) was used. The limit of quantification of human insulin was 4.3 μU/ml, with a working range of 4.3–138 μU/ml.

Statistics

Pharmacodynamics was analyzed by ANOVA with subject, treatment, sequence group, and period effects on untransformed data for BG-$AUC_{0–2h}$, BG-$AUC_{0–6h}$, BG_{max}, ΔBG_{max}, and BG_{min}; 95% CIs were calculated for the respective mean ratios of all pairwise treatment comparisons using Fieller's theorem. ΔBG-t_{max} and BG-t_{min} were analyzed using nonparametric methods, and 95%

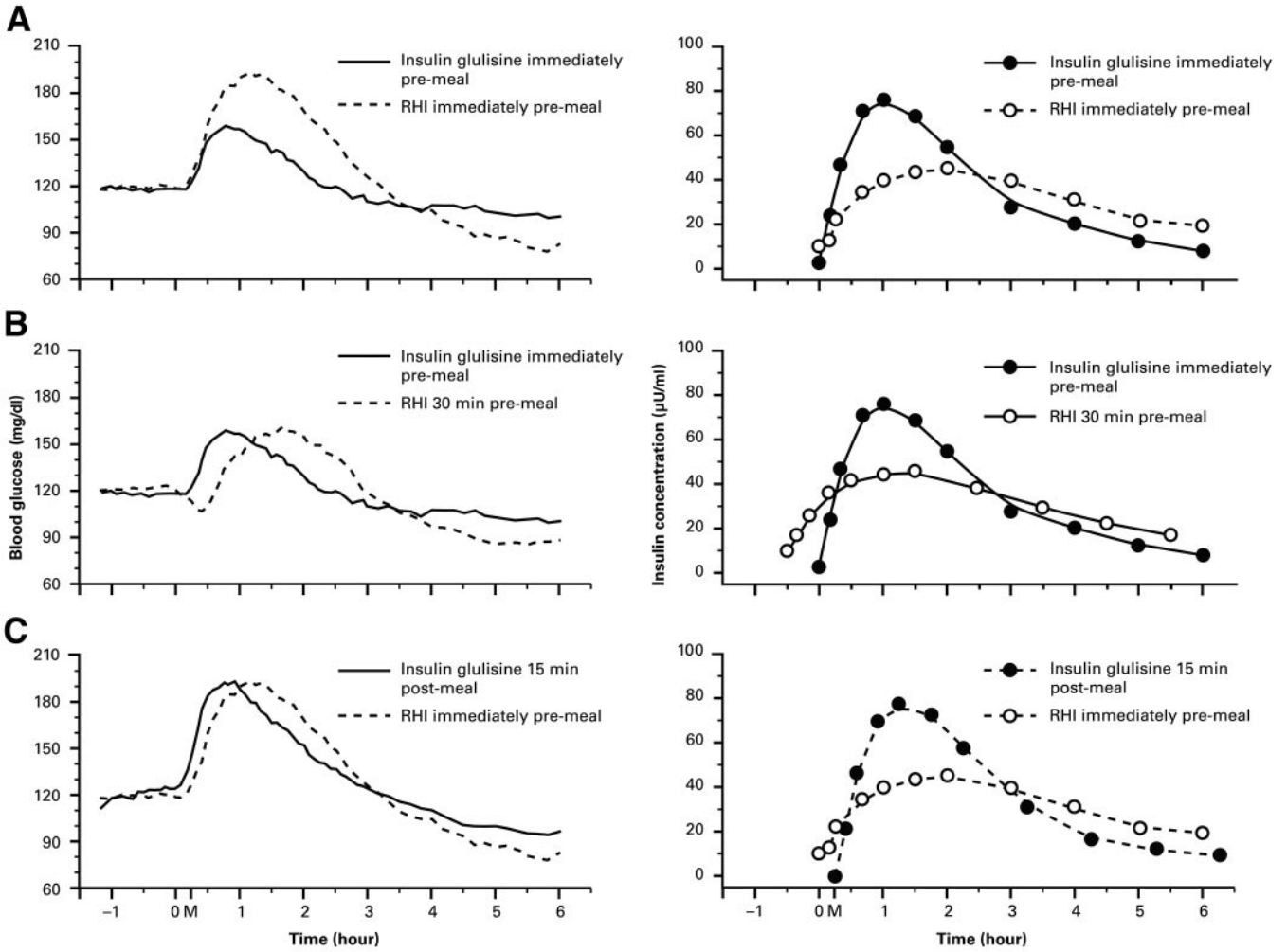

Figure 1— *Blood glucose concentrations (milligrams per deciliter; LOESS averaged) and serum insulin concentrations (microunits per milliliter; LOESS averaged) after administration of insulin glulisine injected immediately premeal compared with RHI injected immediately premeal* (A)*, insulin glulisine injected immediately premeal compared with RHI injected 30 min premeal* (B)*, and insulin glulisine injected 15 min postmeal compared with RHI injected immediately premeal* (C)*. 0, start of meal; M, end of meal. The blood glucose graphs show a LOESS smoothed minute-by-minute recording;* ○ *and* ● *in the insulin graphs indicate sampling time.*

nonparametric CIs were calculated for the respective median differences in treatments.

Pharmacokinetics was assessed using ANOVA on INS-AUC$_{0-2h}$, INS-AUC$_{0-6h}$, and INS-C_{max}, of natural log–transformed insulin glulisine and RHI concentration data. INS-t_{max} and INS-MRT were analyzed using nonparametric methods. Within-subject variability was assessed as intraindividual coefficient of variation (CV) values, taken from the mean sum of the error terms as calculated by the repeated-measures ANOVA on the raw data for INS-t_{max} and on natural log-transformed values for INS-AUC, INS-C_{max}, and INS-MRT. The statistical *F* distribution was used to calculate 90% CIs for CV% and the comparison of variances between treatments for the ratio of two variances.

RESULTS

Study conduct and subject characteristics

In this study, 2 women and 19 men with type 1 diabetes were enrolled, randomly assigned, and treated. One treated subject was withdrawn due to an adverse event (acute bronchitis), which occurred during the first study period; this subject was replaced. Thus, a total of 20 subjects completed the study as per protocol (not including the withdrawn subject) and were included in the pharmacokinetic/pharmacodynamic analyses, whereas all 21 subjects (including the withdrawn subject) who received treatment were included in the safety analyses. The mean age of enrolled subjects at baseline was 36 ± 9 years (range 21–53), the mean weight was 84 ± 14 kg (range 62–108), the mean BMI was 26.0 ± 2.6 kg/m^2 (range 22.1–31.9), and the mean A1C level was 7.8 ± 1.0% (range 6.3–9.4)

Pharmacodynamics

Pharmacodynamic data are summarized in Table 1 and are presented graphically in Fig. 1. The mean baseline blood glucose concentrations were similar at all treatment visits: 119 mg/dl (6.6 mmol/l) for immediately premeal insulin glulisine, 124 mg/dl (6.9 mmol/l) for postmeal insulin glulisine, 120 mg/dl (6.7 mmol/l) for premeal RHI (−30 min), and 120 mg/dl (6.7 mmol/l) for immediately premeal RHI.

Insulin glulisine provided tighter blood glucose control than RHI when both were given immediately premeal (Fig. 1*A*). Blood glucose exposure within 2 h after the start of the meal, BG-

AUC_{0-2h}, was significantly lower (279 vs. 334 mg · h/dl), and BG_{max} (180 vs. 209 mg/dl) and ΔBG_{max} (65 vs. 89 mg/dl) were lower (although not significantly) with insulin glulisine than with RHI, respectively. In contrast, BG-AUC_{0-6h} for these two treatment groups was not significantly different (insulin glulisine 708 vs. RHI 770 mg · h/dl).

Insulin glulisine given immediately premeal and RHI given 30 min premeal provided comparable blood glucose control (Fig. 1*B*). Both 2- and 6-h blood glucose exposures as well as maximum excursions and maximum concentrations were all well matched (BG-AUC_{0-2h} 279 vs. 261 mg · h/dl, BG-AUC_{0-6h} 708 vs. 715 mg · h/dl, ΔBG_{max} 65 vs. 64 mg/dl, and BG_{max} 180 vs. 177 mg/dl). However, despite premeal onset of activity, treatment with RHI resulted in ΔBG-t_{max} occurring 43 min later compared with insulin glulisine.

Postmeal insulin glulisine and RHI given immediately premeal produced similar effects on postprandial blood glucose exposure and excursion (BG-AUC_{0-2h} 337 vs. 334 mg · h/dl, BG-AUC_{0-6h} 777 vs. 770 mg · h/dl, BG_{max} 208 vs. 209 mg/dl, and ΔBG_{max} 85 vs. 89 mg/dl), although ΔBG-t_{max} was later by 33 min with RHI (Fig. 1*C*).

Regardless of injection time, the average BG_{min} occurred toward the end of the 6-h observation period and was below baseline values with either insulin. However, BG_{min} was greater by up to 10 mg/dl and earlier by up to 40 min (t-BG_{min}) with insulin glulisine, compared with RHI.

Pharmacokinetics

Pharmacokinetic data are summarized in Table 2 and are also presented graphically in Fig. 1. Insulin glulisine was absorbed more rapidly and reached a mean INS-C_{max} that was almost twice as large as the INS-C_{max} for RHI (immediately premeal insulin glulisine 82 μU/ml, postmeal insulin glulisine 79 μU/ml vs. immediately premeal RHI 45 μU/ml; 30-min premeal RHI 46 μU/ml). In addition, median INS-t_{max} for insulin glulisine was half of that for RHI (immediately premeal insulin glulisine 55 min, postmeal insulin glulisine 57 min vs. immediately premeal RHI 97 min; 30-min premeal RHI 82 min) at equal total systemic exposure (INS-AUC_{0-6h}). Absorption and elimination of insulin glulisine and RHI were both unaffected by the timing of injection relative to meal intake.

Table 2—*Pharmacokinetic data of insulin glulisine and RHI injected before and after a meal*

	Insulin glulisine		RHI		Point estimate (90% CI)*	
	Immediately premeal (A)	15 min postmeal (B)	30 min premeal (C)	Immediately premeal (D)	Insulin glulisine (*A*)/insulin glulisine (B)	Insulin glulisine(*A*; B)/RHI (C; D) (two visits combined) / RHI (C)/RHI (D)
INS-$AUC_{(0-2h)}$ (μIU · min/ml)	7,278	6,959	4,258	4,091	105 (95–116)	104 (94–115)
CV (90% CI) (%)	15 (10–0)		12 (8–16)			171 (154–189)
INS-$AUC_{(0-6h)}$ (μIU · min/ml)	11,912	11,897	11,550	11,531	100 (92–110)	100 (92–110)
CV (90% CI)	9 (6–12)		9 (6–12)			103 (93–114)
INS-C_{max} (μIU/ml)	82	79	46	45	103 (93–114)	103 (93–114)
CV (90% CI)	17 (11–22)		12 (8–16)			177 (160–196)
INS-t_{max} (min)	55†	57†	82†	97†	−4 (−7 to 0)‡	−12 (−27 to 7)‡
CV (90% CI) (%)	12 (8–16)		35 (23–46)			−39 (−46–−35)‡
INS-MRT (min)	98†	99†	161†	168†	−7 (−14 to 0)‡	−4 (−8 to 1)‡
CV (90% CI) (%)	15 (8–16)		6 (4–7)			−61 (−68 to −54)‡

Values are geometric means or †median values. *Point estimates and 90% CIs for the ratio of treatment means, based on natural log-transformed data, expressed as percentages. ‡Point estimates and 90% CIs for the respective median differences, from nonparametric data analysis.

Within-subject variability of pharmacokinetic data

Within-subject variability of total insulin exposure (INS-AUC_{0-6h}) between treatment groups was low and similar for insulin glulisine and RHI, whereas variability in INS-t_{max} was markedly less for insulin glulisine versus RHI, as expected (Table 2). Variability in INS-MRT, however, was lower for RHI compared with insulin glulisine.

Safety assessments

There were no serious adverse events reported. Eleven nonserious adverse events were reported in eight subjects but were not deemed to be related to the study treatments. One subject withdrew because of acute bronchitis. This event occurred 6 days after treatment with insulin glulisine and, again, was deemed to be unrelated to the study medication. Mild-to-moderate headache was the most frequent adverse event reported (five events in three subjects).

There were no clinically relevant abnormalities in any of the laboratory variables examined. No subjects reported any pain at the site of injection, and local tolerance was good.

CONCLUSIONS — In this study, we compared insulin glulisine, administered immediately before or immediately after a 15-min meal, with RHI administered either 30 min before or immediately before a meal, in terms of postprandial blood glucose control. Insulin glulisine disposed the same amount of glucose as RHI but achieved this in a shorter time, thus providing a better match to the physiologic glucose load profile. As a consequence, postprandial blood glucose control with insulin glulisine given immediately before a meal appeared to be advantageous compared with RHI given 30 min before a meal (as recommended [4]) and was superior to RHI given immediately before a meal (as is frequent practice [5,6]). In addition, insulin glulisine administered 15 min after a meal provided a similar level of postprandial blood glucose control as that seen with RHI given immediately before a meal. Although late-onset hypoglycemia occurred with both insulins, the minimal blood glucose concentration was greater by 10 mg/dl with insulin glulisine compared with RHI, indicating that hypoglycemic side effects are less likely to occur with insulin glulisine use.

These findings may be explained by the more rapid absorption of insulin glulisine, which was present at maximum concentrations that were almost twice as large as those seen with RHI, in approximately half the time, with less variability, and at otherwise equal total systemic insulin exposure. Moreover, the lasting blood glucose–lowering effect of RHI, which extends beyond postmeal carbohydrate absorption, may account for the difference in late-onset hypoglycemia, predicted by the higher minimal postmeal blood glucose concentration observed with insulin glulisine.

Insulin glulisine demonstrates an absorption and action profile that more closely resembles physiologic insulin secretion in response to a meal, as shown with other insulin analogs (i.e., insulin lispro and insulin aspart) (10–18). Such a profile would be expected to correlate with an improvement in long-term glycemic control compared with RHI. However, the hypothesis that a reduction in postprandial hyperglycemia (when using rapid-acting analogs such as insulin lispro or insulin aspart) is accompanied by parallel improvements in blood glucose control in the long-term was not substantiated by corresponding reductions in A1C (19). This result was attributed to less-than-optimal basal insulin replacement or already adequate baseline glycemic control (20). Indeed, appropriate titration only and careful between-meal adjustment of NPH insulin rendered long-term insulin lispro superior to RHI in terms of A1C reduction at lower incidences of hypoglycemia (21). For perspective, premeal insulin glulisine plus less complex basal insulin coverage with insulin glargine is associated with a greater reduction in A1C compared with that seen with RHI plus glargine given as recommended in patients with type 1 diabetes (22).

Although the injection of insulin glulisine before meals afforded the best glycemic control, postmeal administration of insulin glulisine was at least as effective as premeal RHI, in agreement with observations already made previously with insulin lispro (18). Indeed, long-term postmeal administration of insulin glulisine combined with insulin glargine was noninferior to RHI plus glargine given as recommended (22), unlike insulin lispro when combined with insulin ultralente (23). As postmeal administration allows for adjustment of insulin doses depending on the composition and size of the meal, it may provide more flexibility, potentially resulting in tighter glycemic control and improved quality of life outside clinical trials (14,24). An increased flexibility in meal-injection intervals may be particularly relevant for children who have less predictable daily activities and require greater treatment flexibility to achieve and maintain glycemic control. Indeed, preliminary data in children and adolescents confirm improved postprandial glucose control with insulin glulisine treatment (25).

RHI, when given as recommended (30 min before a meal), may meet postprandial insulin demand but may, at the same time, increase the risk of premeal hypoglycemia (Fig. 1*B*). This effect can be critical when patients delay their meals or if the dosing-meal interval is inappropriate. In fact, previous studies have shown that excessive intervals between the insulin injection and the start of a meal may increase the frequency of hypoglycemic events (18,26). It is important to note that in the present study, such premature blood glucose reductions were noticed with RHI administered 30 min premeal (Fig. 1*B*) but were not seen with immediate premeal injections of insulin glulisine.

Across a range of studies, there is some evidence to suggest that with slightly abnormal (but still low) A1C values (as in the early stages of diabetes), postprandial hyperglycemia adds more to the total hyperglycemic burden and associated cardiovascular risk than at later disease stages with very abnormal values to which elevated basal postabsorptive glucose concentrations contribute more (27–29). More recent evidence suggests that, in addition to an existing risk of chronic hyperglycemia, excessive postprandial excursions may provide additional risks for the actual development of cardiovascular diseases (30,31). However, it is still uncertain whether postprandial hyperglycemia is just a marker of the risk rather than related causally to cardiovascular outcomes (32). If true, rapid-acting insulin analogs, such as insulin glulisine, providing improved postprandial glycemic control, as shown by lower postprandial blood glucose excursions compared with RHI, may therefore help to reduce the risk of cardiovascular complications and even mortality over and above that conferred by improving long-term glycemic control (33). This hypothesis, of course, needs to be confirmed in adequately designed long-term studies.

In summary, insulin glulisine provided better physiologic postprandial glu-

cose control by disposing of glucose more rapidly than RHI, in subjects with type 1 diabetes. Administration of insulin glulisine immediately before a meal resulted in greater glucose disposal compared with that provided by RHI injection exactly 30 min before a meal. By reducing postprandial hyperglycemia, insulin glulisine may help to reduce the risk of micro- and macrovascular complications.

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