Dose-Response Relationship of Insulin Glulisine in Subjects With Type 1 Diabetes

REINHARD H.A. BECKER, MD[1]
ANNKE D. FRICK, PHD[1]
LESZEK NOSEK, MD[2]
LUTZ HEINEMANN, PHD[2]
KLAUS RAVE, MD[2]

Rapidly absorbed and acting insulin analogs are increasingly being used to improve postprandial metabolic control (1), which may help in reducing cardiovascular-related and all-cause mortality in patients who already have good metabolic control (A1C <8%) (2). Insulin glulisine is a new insulin analog (3) and, unlike other insulin analog products, is formulated without added zinc to achieve sufficient physical shelf life (4). This unique formulation allows for the immediate availability of monomeric and dimeric insulin glulisine molecules after injection, which is key for rapid absorption into the blood stream from subcutaneous tissue (5). Pharmacokinetic, pharmacodynamic, and safety studies of insulin glulisine in healthy volunteers and patients with diabetes have shown that subcutaneous injection of insulin glulisine more closely mimics physiologic postprandial insulin action than regular human insulin (RHI) (6). Indeed, superior metabolic control was achieved with insulin glulisine compared with RHI in subjects with type 1 diabetes on effectively titrated basal insulin regimens (7). However, despite the increasing use of rapid-acting insulin analogs, surprisingly little is known about dose escalation on systemic insulin concentrations and metabolic activity in subjects with diabetes. This study was conducted to investigate the dose-exposure and dose-response relationships of insulin glulisine compared with RHI in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

In a single-center, randomized, euglycemic, glucose clamp trial, 18 male patients with type 1 diabetes were included in the study (aged 35.0 ± 9.2 years, BMI 24.5 ± 2.7 kg/m^2, A1C 7.7 ± 0.9%). The study included a screening visit, three glucose clamp visits with insulin glulisine, three glucose clamp visits with RHI, and a follow-up visit.

Basal insulin supplementation was replaced with short-acting insulin for a minimum of 24 h before the study began. Subjects were attached to a Biostator (Life Science Instruments), and overnight blood glucose levels were manually maintained at 80–150 mg/dl (4.4–8.3 mmol/l) with intravenous RHI infusion (Insuman Rapid U100; sanofi-aventis). On the morning of treatment, blood glucose was adjusted to 100 mg/dl (5.5 mmol/l) before medication and maintained throughout the euglycemic clamp with an algorithm-based automated infusion of 20% glucose solution. Intravenous RHI infusion was discontinued immediately before the injection of insulin glulisine or RHI in a preset sequence of doses (0.075, 0.15, or 0.3 units/kg body wt). The glucose clamp was stopped when blood glucose levels reached ≥180 mg/dl (≥10 mmol/l) for 30 min in the absence of an intravenous glucose infusion (end-of-dose phenomenon) or after 10 h, depending on which came first. Insulin was sampled at predefined times, while blood glucose and glucose infusion rates (GIRs) were recorded throughout the glucose-clamp period on a minute-to-minute basis by the Biostator and the data smoothed.

Both insulin exposure and metabolic response were tested for strict monotonic increases with dose. Dose proportionality was assessed by pairwise dose comparisons for early insulin exposure (INS-AUC [area under the curve]$_{0-2h}$), total insulin exposure (INS-AUC$_{total}$), maximal insulin concentration (INS-C$_{max}$), early glucose disposal (GIR-AUC$_{0-2h}$), total glucose disposal (GIR-AUC$_{total}$), and maximal effect (GIR$_{max}$). Point estimates (PEs) and 95% CIs for the ratio of treatment means were calculated for the doses of 0.075 units/kg versus 0.15 units/kg and 0.15 units/kg versus 0.3 units/kg. Dose proportionality within the commonly accepted bioequivalence criteria (0.80–1.25) was confirmed when the 95% CI range for a treatment ratio was within 1.6–2.5.

RESULTS

All subjects maintained euglycemia at 100 mg/dl (5.5 mmol/l) for the duration of the clamp, except for three subjects on 0.075 units/kg RHI who demonstrated transient blood glucose elevations (<130 mg/dl [7.2 mmol/l]) in the absence of glucose infusion (data not shown). Figure 1 displays the time-concentration and time-action profiles after subcutaneous injection of 0.075, 0.15, and 0.3 units/kg insulin glulisine and RHI. Insulin glulisine and RHI showed dose-proportional increases in the dose ranges 0.075, 0.15, and 0.3 units/kg for INS-AUC$_{total}$ (PE [95% CI] for treatment ratios 0.15/0.075 and 0.3/0.15 units/kg: 2.1 [2.0–2.2] and 2.2 [2.1–0.3] vs. 1.8 [1.6–2.0] and 2.0 [1.8– 2.2], respectively) and INS-C$_{max}$ (1.7 [1.6–1.9] and 2.0 [1.8–2.1] vs. 1.7 [1.6–1.9] and 1.8 [1.6–2.0], respectively). However, at all doses, insulin glulisine was about twice as rapidly absorbed as RHI (INS-AUC$_{0-2h}$: 3,792, 6,676, and 12,992 vs. 2,211, 3,448, and 5,792 $\mu U \cdot min \cdot ml^{-1}$; $P <$ 0.05) and reached maximal serum concentrations in about one-half the time (INS-T$_{max}$: 47, 57, and 72 vs. 82, 104, and 119 min; $P < 0.05$). Corresponding glucose disposition for insulin glulisine

From [1]sanofi-aventis, Frankfurt/Main, Germany; and the [2]Profil Institute for Metabolic Research, Neuss, Germany.
Address correspondence and reprint requests to Reinhard Becker, MD, sanofi-aventis, Building H831, Room C 0441, Frankfurt, Germany. E-mail: reinhard.becker@sanofi-aventis.com.
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Abbreviations: AUC, area under the curve; GIR, glucose infusion rate; PE, point estimate; RHI, regular human insulin.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

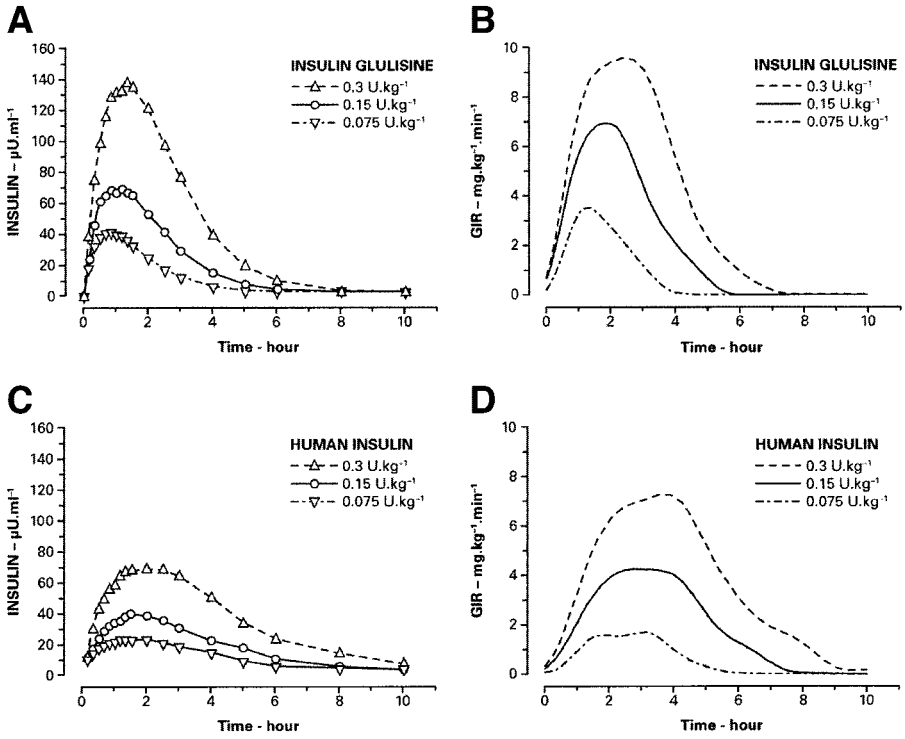

Figure 1—*Time-concentration* (A *and* C) *and time-action* (B *and* D) *profiles of 0.075 units/kg (dashed and dotted lines), 0.15 units/kg (solid line), and 0.3 units/kg (dashed line) insulin glulisine* (A *and* B) *and regular human insulin* (C *and* D) *after subcutaneous injection in subjects with type 1 diabetes.*

was twice as large within 2 h after injection than with RHI (GIR-$AUC_{0–2h}$: 314, 491, and 536 vs. 127, 219, and 294 mg/kg; $P < 0.05$) but was similar in extent on completion (GIR-AUC_{total}: 499, 1,090, and 1,476 vs. 416, 1,076, and 1,555 mg/kg; P = NS). End-of-dose phenomena were observed earlier with insulin glulisine by ~1.5–2.5 h at any dose (7.5, 9.1, and 9.6 h for insulin glulisine and 9.2, 9.5, and 10.0 h for RHI). A monotonically increasing dose-response relationship in GIR-AUC_{total} was observed in 16 of 18 subjects for either insulin, but dose proportionality was only shown for the dose range 0.075–0.15 units/kg with insulin glulisine (PE 2.2 [95% CI 1.7–2.9]) but not with RHI at any treatment ratio. In contrast, only five to six subjects displayed individual dose separation for GIR-$AUC_{0–2h}$ with each step and insulin. All subjects completed the six trial visits without clinically relevant adverse events. Three instances of headaches occurred with the highest dose of insulin glulisine.

CONCLUSIONS — In the absence of basal insulin supplementation, this Biostator-based, euglycemic, glucose clamp study in subjects with type 1 diabetes showed dose-proportional exposure of clinically relevant doses (0.075, 0.15, and 0.3 units/kg corresponding to 6, 12, and 24 units for an 80-kg subject) of a rapidly absorbed and acting insulin analog, insulin glulisine, and RHI. This is accompanied by dose proportionality in total metabolic response between 0.075 and 0.15 units/kg for insulin glulisine only and less than proportional increment with the large dose (0.3 units/kg) for either insulin. This indicates saturation of efficacy for both insulins and implies that a substantially larger than twofold increase in insulin dose is necessary to achieve a doubling of the metabolic effect with high doses.

For reliable dosing, there should be no substantial shift in the absorption and action profile with increasing doses. The data confirm that insulin glulisine at any dose is absorbed approximately twice as fast and takes effect twice as rapidly compared with RHI, while disposing the same quantity of glucose as RHI at any dose.

In conclusion, insulin glulisine presents rapid, dose-proportional absorption, resulting in saturable dose-proportional glucodynamic activity in subjects with type 1 diabetes, allowing predictable control of postprandial hyperglycemia.

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