Pharmacokinetics and Pharmacodynamics of High-Dose Human Regular U-500 Insulin Versus Human Regular U-100 Insulin in Healthy Obese Subjects

AMARO DE LA PEÑA, PHD
MATTHEW RIDDE, MD
LINDA A. MORROW, MD
HONGHA H. JIANG, PHD
HELLE LINNEBEJERG, PHD
ADAM SCOTT, BS

OBJECTIVE—Human regular U-500 (U-500R) insulin (500 units/mL) is increasingly being used clinically, yet its pharmacokinetics (PK) and pharmacodynamics (PD) have not been well studied. Therefore, we compared PK and PD of clinically relevant doses of U-500R with the same doses of human regular U-100 (U-100R) insulin (100 units/mL).

RESEARCH DESIGN AND METHODS—This was a single-site, randomized, double-blind, crossover euglycemic clamp study. Single subcutaneous injections of 50- and 100-unit doses of U-500R and U-100R were administered to 24 healthy obese subjects.

RESULTS—Both overall insulin exposure (area under the serum insulin concentration versus time curve from zero to return to baseline [AUC0–t]) and overall effect (total glucose infused during a clamp) were similar between formulations at both 50- and 100-unit doses (90% [CI] of ratios contained within [0.80, 1.25]). However, peak concentration and effect were significantly lower for U-500R at both doses (P < 0.05). Both formulations produced relatively long durations of action (18.3 to 21.5 h). Time-to-peak concentration and time to maximum effect were significantly longer for U-500R than U-100R at the 100-unit dose (P < 0.05). Time variables reflective of duration of action (late tRmax50, tRmax50) were prolonged for U-500R versus U-100R at both doses (P < 0.05).

CONCLUSIONS—Overall exposure to and action of U-500R insulin after subcutaneous injection were no different from those of U-100R insulin. For U-500R, peaks of concentration and action profiles were blunted and the effect after the peak was prolonged. These findings may help guide therapy with U-500R insulin for highly insulin-resistant patients with diabetes.

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The interrelated epidemics of obesity and type 2 diabetes have led to increasing insulin resistance and insulin dose requirements in insulin-requiring patients. Concentrated beef regular U-500 (500 units/mL) insulin (Iletin; Eli Lilly and Company) was first introduced in the United States in 1952. The current recombinant human regular U-500 (U-500R) insulin preparation (Humulin R U-500; Eli Lilly and Company) entered the U.S. market in 1997. Use of U-500R increased 97% between August 2008 and September 2010 (1), reflecting the increasing number of patients requiring high insulin doses. Clinical case series demonstrate the effectiveness of U-500R in lowering hemoglobin A1c (HbA1c) with low incidence of hypoglycemia and moderate weight gain (2–8).

Despite increasing clinical use, few pharmacokinetic (PK) and pharmacodynamic (PD) studies have been conducted (7,9,10), and scarce PK/PD data are available for the higher doses of U-500R now typically being used in clinical practice (5–8). The primary aim of this study was to evaluate the relative exposure after two clinically relevant doses of U-500R versus U-100 regular human insulin (U-100R) in healthy obese subjects.

RESEARCH DESIGN AND METHODS

Study design

This was a single-center, four-period, four-sequence, crossover, randomized, double-blind euglycemic clamp study. The primary objective was to evaluate the relative exposure (area under the serum insulin concentration versus time curve from zero to return to baseline [AUC0–t]) for U-500R and U-100R after subcutaneous administration of 50- and 100-unit doses in healthy obese subjects. The 50- and 100-unit doses were chosen to approximate 0.4–0.5 and 0.8–1.0 unit/kg insulin doses, respectively (without exceeding 1-mL dosing for U-100R). Secondary aims included comparing other PK and PD parameters between formulations and doses and assessing safety and tolerability of the two treatments and doses in healthy obese subjects. The study was approved by an ethical review board. All study procedures were carried out in

From 1Eli Lilly and Company, Indianapolis, Indiana; the 2Division of Endocrinology, Diabetes, and Clinical Nutrition, Oregon Health and Science University, Portland, Oregon; the 3Profil Institute for Clinical Research, Chula Vista, California; 4Eli Lilly and Company, Erl Wood, U.K.; and 5Lilly USA, Indianapolis, Indiana.

Corresponding author: Amparo de la Pera, de_la_pena_amparo@lilly.com.

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As a phase 1 trial, this study was not registered with an independent clinical trial registry but was listed on the Eli Lilly and Company clinical trial website, http://www.lillytrials.com/initiated/files/12774.pdf.

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compliance with the Declaration of Helsinki and Good Clinical Practices. All subjects provided written informed consent.

**Study subjects**

Eligible subjects were healthy obese men and women of 21–65 years of age, with BMI 30–40 kg/m² and total body weight ≥125 kg. The intent was to recruit subjects with BMIs and weights similar to those typically seen in type 2 diabetes patients who require high-dose insulin treatment (5). Subjects (N = 24) were randomly assigned to one of four dosing sequences: ABCD, BDAC, CADB, and DCBA. Treatments were as follows: A = 50 units U-500R, B = 100 units U-500R, C = 50 units U-100R, and D = 100 units U-100R. All subjects received each of the four treatments on four different occasions. Subjects were instructed to refrain from alcohol and vigorous exercise in the 24 and 48 h, respectively, before each clamp; to fast 8 h before dosing and during each clamp; and to refrain from smoking during study visits.

Exclusion criteria included systemic glucocorticoid use within 3 months before screening and excessive alcohol use (>21 beers/week for men or 14 beers/week for women or unwillingness to stop alcohol consumption for 24 h before each study visit). Subjects were also excluded if they had elevated fasting glucose or impaired glucose tolerance (i.e., prediabetes [11]) as assessed by fasting blood glucose (BG) and oral glucose tolerance testing.

**Euglycemic glucose clamp procedure**

Clamp procedures were separated by periods of at least 7–21 days, and a follow-up visit occurred 7–28 days after visit 4. At the start of each clamp, each subject’s fasting BG was measured three times, and the results were averaged to achieve a baseline BG concentration. The BG concentration target during the clamp procedure was set at 5 mg/dL (0.3 mmol/L) below the subject’s baseline BG concentration.

Insulin was administered subcutaneously in alternating lower abdominal quadrants with conventional U-100 insulin syringes with 8-mm 31-gauge needles. With the exception of the qualified site personnel/pharmacists who were involved in the study insulin preparation and administration, the subjects, investigator, and all other site personnel responsible for collecting and/or assessing adverse events (AEs) and site staff operating the glucose clamps were masked to the study treatments. To ensure masking, the entire length of the syringes was covered with an opaque label. Doses were then administered by masked site personnel.

Subjects underwent euglycemic clamps for up to 24 h using the Biostator (Life Science Instruments, Elkhart, IN) automated glucose clamp device (12). The Biostator automatically calculated the appropriate adjustment to the intravenous infusion rate of a 20% glucose solution needed to maintain the subject’s BG concentration within 5% of the target. Glucose infusion rates (GIR) and BG values were recorded once a minute.

Safety was assessed throughout the study by monitoring adverse events and concomitant medications, physical examinations, clinical laboratory tests, and vital sign measurements.

**PK and PD analyses**

PK and PD analyses were performed on all subjects completing at least one clamp procedure.

Blood samples for the determination of serum immunoactive insulin concentrations were collected at specified intervals throughout the clamp. Insulin concentrations were determined by radioimmunoassay validated over the range of 34–2,870 pmol/L (Alta Analytical Laboratory, San Diego, CA). Estimates of PK parameters were calculated by standard noncompartmental methods of analysis using WinNonlin Enterprise Version 5.0.1 (Pharsight, Mountain View, CA). These included the area under the serum insulin–time curve from zero to return to baseline (AUCO-CR), maximum serum insulin concentration (Cmax), time of maximum serum insulin concentration (tmax), and the apparent terminal half-life (t1/2).

Relative exposure, defined as the ratio of AUC0–Cmax of U-500R versus U-100R formulations, was assessed using a linear mixed-effects model, which included treatment, period, and sequence as fixed effects and the subject as a random effect. The response variables AUCO–Cmax and Cmax were log-transformed due to their nonnormal distribution and analyzed separately. The difference in treatments (50 units U-500R minus U-100R, or 100 units U-500R minus U-100R) was back-transformed along with the 90% CI. The estimated difference in time of occurrence of tmax was analyzed using the nonparametric Wilcoxon signed rank test.

A locally weighted scatterplot smoothing (LOESS) function in S-PLUS version 7.0 for Windows (Insightful, Somerville, MA) was used to fit the GIR data. PD parameters, including maximum GIR (Rmax), time of maximum GIR (tRmax), amount of glucose infused (Gmax), and times of half-maximum GIR before and after Rmax (early and late tRmax) were calculated based on the individual LOESS-fitted data. The time of the first change in the non-zero GIR (tRmax) and the time of the last non-zero GIR (tRmax) were determined from the raw GIR data. The main PD parameters (Gmax and Rmax) were log-transformed prior to analysis due to their nonnormal distribution and used the linear mixed-effects model as described for PK data. Analyses of tRmax, tRmax, time of first change in GIR, and early and late tRmax were performed using a similar linear mixed-effects model without log-transforming the data.

Supplementary Figs. 1 and 2, which illustrate several PK and PD parameters referred to in this article, are provided for informational purposes.

**RESULTS**—Subjects’ baseline characteristics are shown in Table 1. Patients were similar in age and BMI across sequence groups. Mean insulin dose was 0.5 units/kg (range = 0.4 to 0.6 units/kg) for subjects receiving 50 units of insulin and 1.0 units/kg (range = 0.8 to 1.3 units/kg) for subjects receiving 100 units of insulin.

For the PK primary objective, overall insulin exposure based on AUC0–Cmax was similar between formulations at both 50-unit and 100-unit doses (Table 2 and Fig. 1). The U-500R Cmax was significantly lower relative to U-100R at both doses. The tmax was significantly longer for U-500R versus U-100R only at the 100-unit dose. At the 50-unit dose,

| Table 1—Subject baseline characteristics |
|------------------------------------------|
| Characteristic                           | Subjects |
| Age (years)                              | 39.6 ± 12.1 |
| Men/women                                | 14/10     |
| Race (n [%])                             |           |
| Asian                                    | 1 [4.2]   |
| African American                         | 5 [20.8]  |
| White                                    | 18 [75.0] |
| Weight (kg)                              | 98.1 ± 12.9 |
| Height (cm)                              | 168.7 ± 10.4 |
| BMI (kg/m²)                              | 34.4 ± 2.6 |

Data presented are mean ± SD, with the exception of the men/women data, which are presented as n/total.
apparent $t_{1/2}$ was 4.6 h for U-500R versus 3.9 h for U-100R; and at the 100-unit dose, apparent $t_{1/2}$ was 4.4 h for U-500R versus 3.3 h for U-100R. In general, PD responses were consistent with PK; $G_{\text{tot}}$ for U-500R was similar to U-100R at both doses (Table 2 and Fig. 1). $R_{\text{max}}$ was lower for U-500R versus U-100R at both doses, whereas $t_{\text{Rmax}}$ was shown to be prolonged for U-500R versus U-100R only at the 100-unit dose. Time variables reflective of duration of action (early and late $t_{\text{Rmax}}$, $t_{\text{Rlast}}$) were prolonged for U-500R versus U-100R at both doses. The $t_{\text{onset}}$ was similar for the two doses and formulations.

**Safety**
The most common treatment emergent AEs reported were headache (17 instances reported by 12 subjects) and nausea (5 instances reported by 2 subjects). Incidence of nausea was similar across all doses and formulations. Headache occurred most frequently after the administration of 100 units of U-100R (7 subjects) and least frequently after the administration of 50 units of U-500R (1 subject). No severe treatment emergent AEs were reported, and no subjects discontinued because of AEs. One subject discontinued early because of subject decision. Two subjects were unable to complete one or more clamp procedures as a result of poor venous access.

**CONCLUSIONS**—Different U-500 formulations of regular insulin have been available for more than 50 years and have been used for treatment of patients with severe insulin resistance. However, no studies have compared the PK and PD characteristics or clinical differences of U-100 versus U-500 insulins in obese subjects at these high doses. A clear advantage of U-500R over U-100R insulin for severely insulin-resistant patients is the ability to deliver large doses with a single injection of a smaller volume (less than 1.0 mL, the capacity of the usual insulin syringe). The resulting need for fewer injections might lead to better adherence with a prescribed regimen. Other possible benefits proposed have been better absorption (5) and longer duration of action, compared with U-100R insulin.

An inverse relationship between concentration of injected insulin and its rate of absorption has been suggested in both animal and human studies (13,14). Galloway et al. (15) studied pork regular insulin (at 0.25 units/kg) in healthy nonobese subjects demonstrating no statistically

### Table 2—PK and PD results

|                | 50-unit dose |                | 100-unit dose |                |
|----------------|--------------|----------------|--------------|----------------|
|                | U-100R       | U-500R         | U-100R       | U-500R         |
| PK parameters  |              |                |              |                |
| $AUC_{0-\infty}$ (pmol·h/L) (%) | 6.960 (27) | 6.430 (24) | 8.09 (33) | 3.00 (50) |
| $C_{\text{max}}$ (pmol/L) (%) | 809 (33) | 548 (22) | 504 (75) | 1.00 (4.00) |
| $t_{\text{max}}$ (h) | 3.00 (1.00–8.00) | 4.00 (0.50–8.00) | 3.00 (50–8.00) | 1.00 (1.45) |
| PD parameters  |              |                |              |                |
| $R_{\text{max}}$ (mg/min) | 237 (28) | 419 (28) | 42 (22) | 62 (22) |
| $t_{\text{Rmax}}$ (h) | 1.00 (1.00–4.00) | 0.78 (0.11–1.45) | 0.69 (0.41–0.94) | 0.86 (0.60–1.20) |
| $R_{\text{max50}}$ (mg/min) | 1.69 (33) | 1.41 (21) | 0.78 (0.43–1.19) | 0.86 (0.60–1.20) |
| $t_{\text{Rlast}}$ (h) | 18.5 (20) | 17.3 (20) | 18.5 (20) | 17.3 (20) |
| Values are presented as geometric mean and CI (%), with the exception of $t_{\text{max}}$, which is presented as median (range). $p < 0.05$, treatment of U-500R, difference of LS means (U-500R–U-100R)
significant PK differences in serum insulin concentrations as insulin formulation concentrations increased from U-40 to U-500; however, the time-to-peak BG response was significantly delayed by increasing insulin concentrations. Injection volume may also play a role in absorption rate, with higher volumes of insulin having a smaller percentage of the dose absorbed (13,16). However, for regular insulin, increasing concentrations may be only partially counterbalanced by decreased volume (17,18).

Prior studies of U-100R and other insulins have shown dose dependence of PK characteristics, but there have been no studies performed at these higher dose levels for U-100R or U-500R (19–21). A recent PK/PD study of U-100 lispro in bolus doses up to 50 units in obese patients with type 2 diabetes and insulin requirements ≥100 units/day showed slower absorption and reduced bioavailability (22). Limited PK/PD data have been reported from an exploratory clamp study after administration of a single low dose (0.2 units/kg) of U-500R in three nonobese subjects (t\text{onset} = 30 min, t\text{max} = 1.75 to 4 h, t\text{Rmax} = 6.5 to >10 h) (9). A study in two obese healthy subjects reported (t\text{onset} = 45 min, t\text{max} = 7 to 8.5 h, and t\text{Rmax} = 11.5 h) (10). However, both these studies lacked a direct comparison with U-100R. Another PK study in nine severely insulin-resistant obese patients with type 2 diabetes (total daily dose, 333 units) demonstrated a brisk rise in serum insulin by 30 min and peak mean insulin levels at 5 h with persistent elevation of insulin levels at 7 h after a subcutaneous 100-unit morning dose of U-500R (7).

Our present study confirms some of the expectations derived from prior clinical experience (3–5) and preliminary studies. There were clear differences between formulations in the profiles of serum insulin concentrations and the GIRs reflecting insulin action; PD observations were consistent with PK. Despite differences in both the concentrations and volumes injected, the overall effects (G\text{tot}) and exposure to insulin (AUC\text{0–t'}) of the two formulations at equivalent dosages were similar. However, a greater duration of action of U-500R versus U-100R as demonstrated by longer early and late t\text{Rmax50} and t\text{Rlast} is consistent with clinical reports (5–7). A delay in PK (t\text{max}) and PD (t\text{Rmax}) between formulations was observed at the 100-unit dose only. Both formulations showed longer duration of action than the ~8 h considered typical of human regular insulin at a lower dosage. This protraction of action is presumably due mainly to continuing absorption of insulin from the subcutaneous depot, but a contribution from slower clearance under these conditions cannot be ruled out from this study. The time of start of effect (t\text{onset}) was similar for U-500R and U-100R at both doses, indicating that dosing 30 min before the meal is likely appropriate for U-500R, as recommended for U-100R (11,23).

This euglycemic clamp study examined higher doses of short-acting insulin than any study published previously. The narrow BMI range (30 to 40 kg/m²) and exclusion of subjects with prediabetes was designed to reduce variability in subjects’ insulin sensitivity. Obese subjects...
were used since type 2 diabetes patients requiring high dose insulin treatment are often obese.

Limitations of this study include the use of healthy subjects instead of patients with type 2 diabetes and exclusion of individuals with BMI $>$ 40 kg/m$^2$. The highest dose studied here (100 units; 0.8–1.3 units/kg) is at the lower end of reported clinical dosages for highly insulin-resistant type 2 diabetes patients (1.5 to 3.3 units/kg/day) (5–7) and time-action profiles may be different at higher doses of U-500R in such patients. The lack of measurement of C-peptide levels during clampings is another potential limitation; endogenous insulin contributions to PK/PD parameters cannot be directly assessed. However, it is expected that endogenous insulin was suppressed by the high doses of U-500R and U-100R given in this study.

Our findings have potential clinical implications. For example, the delayed time-to-peak and prolonged total duration of action of high-dose U-100R suggests the commonly used 50:50 distribution of basal to prandial components of a basal-bolus regimen may not be appropriate at high dosage. If U-500R is used instead of U-100R, the longer duration of action of U-500R may support its use as multiple daily injections without the use of a basal insulin. A number of case series have been published describing the use of U-500R injected twice daily (4,7) or three times daily (3,5,6) without the use of basal insulin. However, no controlled clinical trials have been conducted to compare the safety and efficacy of multiple daily injections of U-500R with and without a basal insulin.

While a smaller volume insulin injection is a potentially attractive feature of U-500 insulin, it is critical to avoid dose confusion when switching from U-100 insulins or insulin analogs. Currently, U-500R must be delivered either by U-100 insulin syringes with unit markings that represent one-fifth of the actual U-500R dose administered or by tuberculin syringes with markings showing volume in milliliters (3,5,24,25). In addition, great care needs to be taken to monitor for and avoid hypoglycemia, particularly at night, with the use of U-500R (3,5,24,25).

In summary, overall exposure to and action of U-500R insulin after subcutaneous injections were no different from those of U-100R insulin. However, for U-500R, the peaks of both the concentration and action profiles were blunted and the effect after the peak was prolonged. Confirmation of the present findings, particularly the lack of improved absorption/bioavailability of U-500R versus U-100R, in very obese patients with type 2 diabetes would be of interest. Further study with randomized clinical trials is needed to determine the optimal therapeutic application, safety, and efficacy of concentrated U-500R insulin.

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A.d.l.P., M.R., and J.A.J. were instrumental in the design of the study and the manuscript, wrote the manuscript, and approved the final version of the manuscript. H.H.J. designed the statistical analysis plan for the study and data, wrote the manuscript, and approved the final version of the manuscript. H.L. and L.A.M. participated in the design of the study, wrote the manuscript, and approved the final version of the manuscript. A.S. analyzed data, wrote the manuscript, and approved the final version of the manuscript. K.M.W. and M.H. participated in the design of the study, wrote the manuscript, and approved the final version of the manuscript. K.F.M. participated in the design of the study and collection of data, wrote the manuscript, and approved the final version of the manuscript. J.G.J. participated in the design and writing of the manuscript, drafted the first version of the manuscript, and approved the final version of the manuscript.

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