U-500 Regular Insulin: Clinical Experience and Pharmacokinetics in Obese, Severely Insulin Resistant Type 2 Diabetic Patients

Mayer B. Davidson, MD, Maria D. Navar, MSN, NP, Diana Echeverry MD, Petra Duran BS

Charles Drew University
Los Angeles, California

Running Head – U-500 Regular Insulin for Obese Patients

Correspondence to:
Mayer B. Davidson, MD
E-mail address: mayerdavidson@cdrewu.edu

Submitted 10 August 2009 and accepted 1 November 2009.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
**Objective** – To describe the clinical experience and the pharmacokinetics of U-500 regular insulin in severely insulin resistant obese type 2 diabetic patients.

**Research design and methods** – Patients requiring >200 units of insulin with A1C levels >8.0% were switched to U-500 regular insulin. For the pharmacokinetic study, fasting subjects received 100 units of U-500 regular insulin subcutaneously and samples drawn before and every 30-60 minutes for glucose, insulin and C-peptides until glucose fell below 100 mg/dl.

**Results** – U-500 regular insulin doses were adjusted using the same approach as for adjusting NPH insulin doses. Mean values at baseline and at minimum A1C levels, respectively, were, respectively: A1C (%) – 9.9, 7.1; units/kg – 3.2, 3.3; weight (kg) – 98.6, 102.8. Pharmacokinetically, insulin concentrations rose briskly by 30 minutes and remained elevated for at least 7 hours.

**Conclusions** – Uncontrolled severely insulin resistant obese type 2 diabetic patients can be satisfactorily controlled with U-500 regular insulin.
Clinical or severe insulin resistance (as opposed to pathophysiological insulin resistance) is defined as a situation in which a patient requires more than 200 units of insulin daily. Obesity is by far the most common cause. Patients with severe insulin resistance are very difficult to treat successfully. More physicians are using U-500 regular insulin to treat these patients (1,2). Although empirical observations suggest that this concentrated form of regular insulin has a delayed time-course of action, there are no pharmacokinetic studies representing its clinical use. This paper reports our experience with all 11 of our obese patients on U-500 regular insulin and its pharmacokinetics in nine of them.

**RESEARCH DESIGN AND METHODS**

All patients treated with U-500 regular insulin were taking >200 total units of U-100 NPH plus regular insulin per day, had A1C levels >8.0% in spite of working closely with our nurse practitioners for at least six months, had demonstrated willingness to self-measure glucose concentrations at least twice a day and were able to understand the different dosing of U-500 regular insulin. U-500 regular insulin doses were started and changed according to a slight modification of a published algorithm (3). Doses were adjusted to achieve >50% of values before breakfast and supper between 70-130 mg/dl as we typically do with NPH insulin. Six patients had A1C levels exceeding 7.5% with pre-prandial glucose concentrations in the target range. Post-prandial glucose concentrations exceeded 180 mg/dl and were treated with pre-prandial U-100 lispro insulin injected separately aiming for a post-prandial target of <160 mg/dl.

To achieve a fasting plasma glucose (FPG) concentration of >200 mg/dl on the morning of the pharmacokinetic study, patients omitted their prior evening and that morning’s insulin, increased their bedtime snack the evening before and arrived fasting at the Clinical Research Center. One hundred units of U-500 regular insulin were injected subcutaneously and plasma samples for glucose measured immediately by a Yellow Spring Instrument (YSI) were collected 10 minutes before, just before and every 30 – 60 minutes after the injection until glucose concentrations reached <100 mg/dl when the study was stopped and the subject fed. Insulin and C-peptides were measured by ELISA. A1C levels were measured every three to four months. All patients were negative for insulin binding antibodies. The study was approved by the Charles Drew University Institutional Review Board.

**RESULTS**

There were 10 females, 10 Latinos and one African American. At baseline, their mean duration of diabetes was 16.2 years, BMI 37.7, weight 98.6 kg, total U-100 insulin dose 304 units (74% NPH), total units/kg 3.2 and A1C level 9.9%. The minimum (range) A1C achieved was 7.1% (6.0-7.4). A1C levels were <8.0% in 10 of the 11 patients by 3-4 months and in the 11th by six months. The average dose of insulin at the minimum A1C level was 333 units, units/kg were 3.3 and body weight was 102.8 kg. At the time these data were collected, patients had been followed for a mean of 26 months after being switched to U-500 regular insulin. The most recent A1C level was 7.5% (6.1 to 9.1) which was an average decrease of -2.4% (+0.1 to -7.1).

In six patients who received lispro insulin, the mean A1C level before the rapid-acting analogue was introduced was 8.1%. Three and six months later, it was 7.3% and 7.1%, respectively. Surprisingly, the mean pre-prandial dose was only 9.5 units (6-15). Overall, episodes of hypoglycemia (only one severe one because of a missed meal) seemed
less than in our typical insulin-requiring patients.

Insulin, C-peptide and glucose concentrations are shown in the Figure. Glucose concentrations did not fall below 100 mg/dl for three hours in all nine subjects, for four hours in six, for five hours in four, for six hours in three and for seven hours in two. Insulin concentrations rose briskly by 30 minutes and remained elevated up to seven hours later. The increase in the measured levels was of exogenous origin since C-peptide concentrations uniformly fell.

CONCLUSIONS

Substituting U-500 regular insulin for U-100 NPH insulin markedly improved diabetic control in obese, severely insulin resistant type 2 diabetic patients. Since these patients received the same intensity of counseling and insulin dose adjustments when they were taking either U-100 NPH or U-500 regular insulin, their improved control must have been due to the change in insulin preparations. Although initially there was rapid improvement in all patients and the minimum A1C levels achieved were impressive (6.0% to 7.4%), sustaining that improvement was challenging for some. All but one had lower final than initial A1C levels but in three, final values exceeded 8.0%.

The pharmacokinetic data in the Figure show that U-500 regular insulin has a time course very similar to U-100 NPH insulin (4). Although some patients began to meet the end point after three hours and were not sampled later, there is no reason to believe that their insulin concentrations would not have mirrored the patients who continued to be sampled.

Three issues are often raised when switching to U-500 regular insulin is considered; the cost, patient confusion and which syringe to use. The more concentrated preparation is actually cheaper per unit of insulin (1,5,6). Our experienced CDE’s must be comfortable with the patient’s ability to use U-500 regular insulin. Since we use U-100 insulin syringes (tuberculin syringes are not easy to obtain, the needles are larger and using the familiar “units” is less confusing), we provide them with a conversion table between the units of U-100 and U-500 insulins. The written instructions to the patient and on the prescription state the actual number of units prescribed but also include in parenthesis the number of syringe units to which the U-500 insulin should be drawn.

In conclusion, obese, severely insulin resistant, uncontrolled diabetic patients requiring >200 units per day can be satisfactorily controlled on U-500 regular insulin. It requires a cooperative, aware patient and frequent follow-up initially until the dose is stabilized. Using it as one would use NPH insulin is a simple approach which worked well in this small cohort.

ACKNOWLEDGMENTS

Drs Davidson and Echeverry and Ms Duran were supported by NIH grant # U54-RRO-14616.

LEGEND

Figure – Glucose (A), Insulin (B) and C-Peptide (C) concentrations following the subcutaneous injection of 100 units of U-500 regular insulin in fasting, severely insulin resistant, obese type 2 patients. The number of subjects sampled at each time point is shown at the bottom of the figure. The glucose concentrations in the two subjects remaining at 420 minutes were above 100 mg/dl but the Clinical Research Center was closing for the day.
REFERENCES
U-500 Regular Insulin for Obese Patients

A
Glucose (mg/dl)

B
Insulin (µU/ml)

C
C-Peptide (ng/ml)

N = 9 9 9 9 9 6 4 3 2