U-500 Regular Insulin

Clinical experience and pharmacokinetics in obese, severely insulin-resistant type 2 diabetic patients

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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 min 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 were, respectively, A1C 9.9 and 7.1%, 3.2 and 3.3 units/kg, and weight 98.6 and 102.8 kg. Pharmacokinetically, insulin concentrations rose briskly by 30 min and remained elevated for at least 7 h.

CONCLUSIONS — Uncontrolled severely insulin-resistant obese type 2 diabetic patients can be satisfactorily controlled with U-500 regular insulin.

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RESULTS — There were 10 female subjects, 10 Latino subjects, and 1 African American subject. At baseline, their mean duration of diabetes was 16.2 years, BMI 37.7 kg/m², 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 11 patients by 3–4 months and in the 11th patient by 6 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% (6.1–9.1), which was an average decrease of $\sim$2.4% ($\pm$1 to $-$7.1).

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

Insulin, C-peptide, and glucose concentrations are shown in Fig. 1. Glucose
concentrations did not fall below 100 mg/dl for three subjects, for six, for five in four, for six in three, and for seven in two. Insulin concentrations rose briskly by 30 min and remained elevated up to 7 h 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 diabetes 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 (6.0–7.4%), sustaining that improvement was challenging for some. All but one subject had lower final than initial A1C levels, but in three subjects, 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 3 h 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 certified diabetes educators 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 parentheses 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/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 that worked well in this small cohort.

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