Clinical Experience With U-500 Regular Insulin in Obese, Markedly Insulin-Resistant Type 2 Diabetic Patients

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On a clinical basis, severe insulin resistance is defined as a situation in which a patient requires >200 units of insulin daily for >2 days (1). This definition was determined >50 years ago, when it was erroneously believed that the human pancreas secreted ~200 units of insulin a day. Although it is now known that the normal pancreas secretes only 20–40 units of insulin a day, this clinical definition is helpful because it delineates a very small group of patients, many with a number of unusual underlying problems.

In adults, the conditions associated with clinical insulin resistance are gross obesity, severe infection, Cushing's syndrome, acromegaly, hemochromatosis, lipodystrophic diabetes, genetic insulin receptor abnormalities, insulin receptor antibodies, Werner's syndrome (adult form of progeria), insulin degradation at the injection site, and high titers of IgG insulin binding antibodies (immune mediated). Gross obesity is by far the most common condition. Although a recent review (2) discussed the use of U-500 regular insulin in states of severe insulin resistance, no detailed description of how to start and adjust doses of this concentrated form of insulin was given. This article provides a treatment algorithm for the use of U-500 regular insulin and summarizes our experience with obese, markedly insulin-resistant type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— Nine patients with type 2 diabetes from our diabetes clinic (five women and four men [eight Latino and one African American], aged 49.4 ± 10.0 years [mean ± SD], diabetes duration 13.0 ± 7.6 years, BMI 40.0 ± 5.1 kg/m^2) who received U-500 regular insulin for at least 6 months were prospectively studied. One patient left the program for a liver transplant at another hospital 5 months after U-500 insulin was started. Eight patients were tested for insulin binding antibodies, which were undetectable in six and detected in two at levels below those causing immune-mediated insulin resistance (1). The decision to switch to U-500 insulin therapy was the use of >200 units of insulin a day and HbA_{1c} (A1C) levels of >8.5%, despite having been followed at least monthly by specially trained nurses for >6 months to adjust U-100 insulin doses. Five patients were also taking a maximal dose (2 g) of metformin.

The initiation and dose adjustments of U-500 regular insulin are shown in Fig.1. The before-breakfast dose was adjusted based on the before-supper blood glucose level, and the before-supper dose was based on the fasting blood glucose value. Before-bedtime snacks were emphasized. Although Cochran et al. (2) suggested three injections a day if the total dose of U-500 insulin was 300–750 units (and four injections with a total dose of 750–2,000 units), we did not find that necessary. The range of our final dose was 150–625 units with four patients taking 300–625 units.

Changes in weight and insulin dose were analyzed by the Wilcoxon's signed-rank test. Changes in A1C level were analyzed by a one-way repeated-measures ANOVA. Significance was accepted at $P < 0.05$ (two-tailed test).

RESULTS

— As expected with improved control, all patients gained weight from 109.9 ± 26 kg at baseline when U-500 regular insulin was started to 114.6 ± 2.9 kg 6 months later ($P < 0.01$). There was no change in total insulin dose from 289 ± 61 units at baseline to 322 ± 166 units 6 months later ($P = 0.72$). Insulin dose increased in four patients and decreased in five. A1C levels were high and fairly stable during the 6 months before baseline and fell significantly ($P < 0.001$) by 2.5% 6 months later as follows: −6 months, 11.4 ± 1.9; −3 months, 10.8 ± 2.2; baseline, 10.3 ± 1.9; +3 months, 8.1 ± 0.9; and +6 months ($n = 8$), 7.8 ± 0.6.

CONCLUSIONS

— Only a few articles describing U-500 insulin have been published. The patients studied have had immune-mediated insulin resistance (3), lipoatrophic diabetes (2,4), antibodies against the insulin receptor (2), genetic abnormalities of the insulin receptor (2), or obesity (5–9). In two of the latter studies, U-500 insulin was given via an insulin pump (6,8). In contrast to the present study, none of these provided guidelines for adjusting the doses of this very concentrated insulin preparation. Although this preparation of insulin contains no added chemicals or alterations in its amino acid structure to alter its rate of absorption, the high concentration of insulin delays the absorption to yield a time course of action similar to NPH insulin (10), thus allowing dose adjustments in a manner as if the patient were taking NPH insulin twice a day.

The decrease in A1C levels of 2.5% after 6 months in our patients is similar to

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

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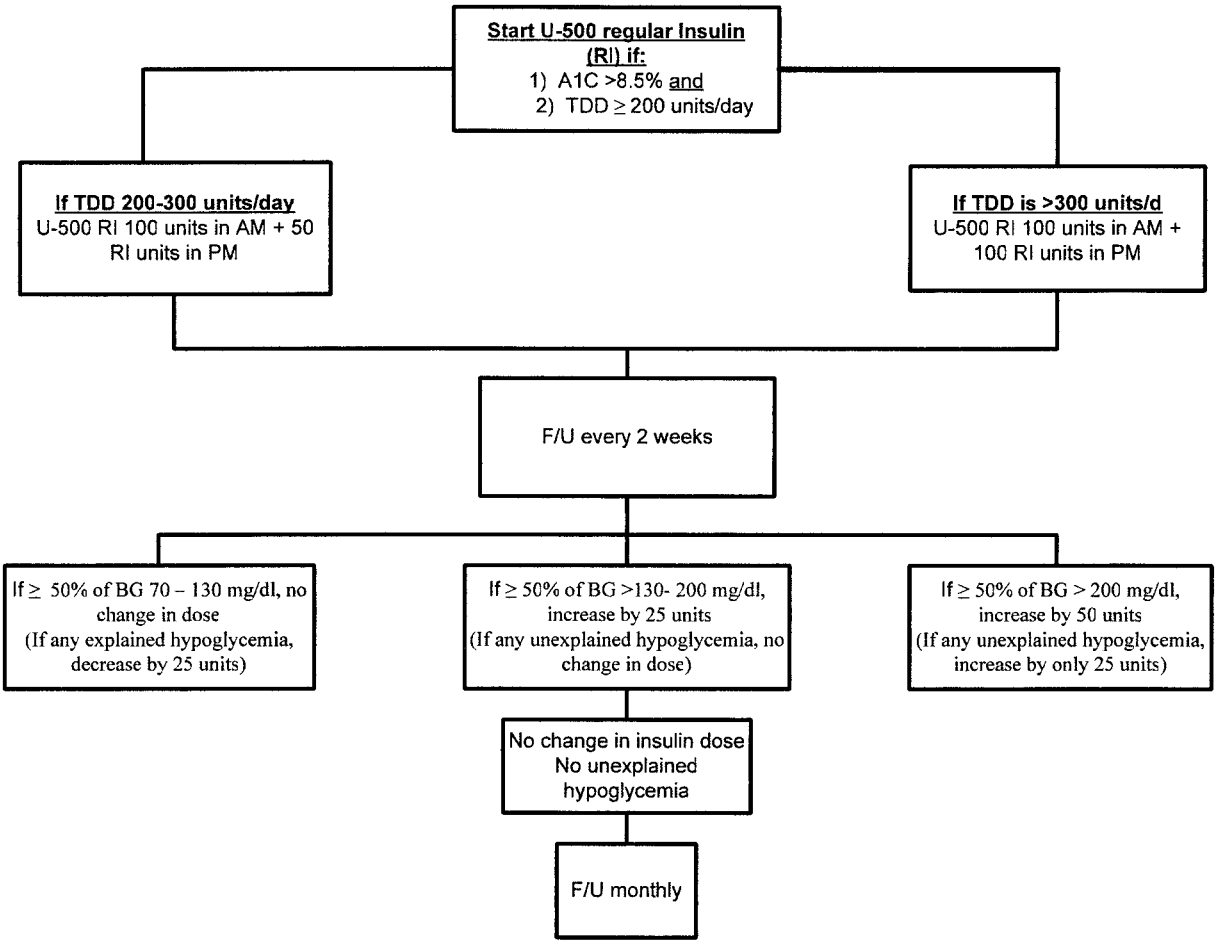

Figure 1—*Algorithm for starting and adjusting U-500 regular insulin doses. Unexplained hypoglycemia are episodes not explained by delayed, smaller-than-usual, or missed meals; increased exercise; or taking incorrect insulin dose. BG, blood glucose; F/U, follow up; TDD, total daily dose.*

the reported experience in obese patients with baseline A1C levels ranging from 9.6 to 10.8% with decreases of 3.2% (6), 1.1% (7), 1.9% (8), and 2.2% (9). Some (7) have suggested the use of tuberculin syringes because it may be easier to explain drawing up the doses in syringes with volume markings rather than unit markings, but the larger needles and difficulty in obtaining these syringes argues against their use. All study participants understood how to use the fivefold more–concentrated insulin preparation. Finally, although 20 ml U-500 regular insulin vials are more expensive than 10 cc U-100 insulin vials, the cost per unit of insulin is less for patients taking such large doses (2,6).

In conclusion, in poorly controlled, obese, type 2 diabetic patients requiring large doses (>200 units a day) of insulin, switching to U-500 regular insulin is both feasible (Fig. 1) and effective.

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References

1. Peters Harmel A, Mathur R: *Davidson's Diabetes Mellitus: Diagnosis and Treatment*. 5th ed. Philadelphia, Elsevier, 2004, p. 133
2. Cochran E, Musso C, Gorden P: The use of U-500 in patients with extreme insulin resistance. *Diabetes Care* 28:1240–1244, 2005
3. Nathan D, Axelrod L, Flier JS, Carr DB: U-500 insulin in the treatment of antibody-mediated insulin resistance. *Ann Intern Med* 94:653–656, 1981
4. Dolberg BK, Lenhard MJ: Successful outcome of pregnancy in a patient with generalized lipoatrophic diabetes mellitus. *Endocr Pract* 6:34–36, 2000
5. Baumann G, Drobny EC: Enhanced efficacy of U-500 insulin in the treatment of insulin resistance caused by target tissue insensitivity. *Am J Med* 76:529–532, 1984
6. Knee TS, Seidensticker DF, Walton JL, Solberg LM, Lasseter DH: A novel use of U-500 insulin for continuous subcutaneous insulin infusion in patients with insulin resistance: a case series. *Endocr Pract* 9:181–186, 2003
7. Neal JM: Analysis of effectiveness of human U-500 insulin in patients unresponsive to conventional insulin therapy. *Endocr Pract* 11:305–307, 2005
8. Lane WS: Use of U-500 regular insulin by continuous subcutaneous insulin infusion in patients with type 2 diabetes and severe insulin resistance. *Endocr Pract* 12: 251–256, 2006
9. Wafa WS, Khan MI: Use of U-500 regular insulin in type 2 diabetes (Letter). *Diabetes Care* 29:2175, 2006
10. Jorgensen KH, Hansen AK, Buschard K: Five fold increase of insulin concentration delays the absorption of subcutaneously injected human insulin suspensions in pigs. *Diabetes Res Clin Pract* 50:161–167, 2000