ORIGINAL ARTICLE

U-500 Insulin as a Component of Basal Bolus Insulin Therapy in Type 2 Diabetes

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Abstract

Background: Changes in hemoglobin A1c (A1C), weight, and total daily insulin dose (TDD) were investigated following initiation of insulin U-500 (U500) alone or as part of a basal/bolus insulin (BBI) regimen.

Subjects and Methods: Records of patients with type 2 diabetes who were prescribed U500 were retrospectively reviewed. Logistic regression analysis was used to investigate relationships between changes in A1C and use of U500 alone or as BBI.

Results: Twelve patients were identified as using U500 alone ($n=2$) or in combination with long-acting (LAI) ($n=7$) or rapid-acting (RAI) ($n=3$) insulin. Reductions in A1C (9.5% at baseline vs. 7.7% at 6–9 months, $P<0.0001$) and increases in weight (128.8 ± 32.7 vs. 131.5 ± 31.3 kg, $P<0.014$) and TDD (260 ± 111 to 333 ± 106 units/day, $P<0.0002$) were observed. Concurrent use of LAI or RAI with U500 did not predict improvements in A1C.

Conclusions: U500 resulted in improvements in A1C and weight gain and increased TDD when used alone or as part of combination insulin therapy. Further investigations to define the optimal use of U500 are recommended.

Introduction

TYPE 2 DIABETES IN OBESE individuals is frequently associated with profound insulin resistance that limits the ability to achieve desired glycemic targets despite multiple daily insulin injections using total daily doses (TDDs) in excess of 200 units/day.^{1,2} In selected patients, U-500 regular insulin (U500) allows for administration of high TDD at volumes lower than that required with standard U-100 insulin (U100) preparations.³ This higher insulin concentration alters the pharmacokinetic properties of regular insulin to that of an intermediate- or long-acting insulin (LAI) preparation.^{4–8}

Standard recommendations for U500 suggest that it be administered in divided doses of two or three injections per day as the sole insulin preparation to meet both basal and meal-related insulin requirements.^{2,3} Others have suggested that it be administered as a component of a basal/bolus insulin (BBI) regimen in combination with either rapid-acting insulin (RAI) or LAI preparations.^{3–7} These suggestions result in uncertainty and variability among clinicians in how to optimally prescribe and implement U500.

The purpose of this investigation was to describe use and patient outcomes with U500 in an outpatient academic specialty diabetes center.

Research Design and Methods

This retrospective study was approved by the University of Pittsburgh Institutional Review Board. All patients with type 2 diabetes identified in the electronic medical record (Epic-Care, Verona, WI) as using U500 between 2003 and 2009 who had a hemoglobin A1c (A1C) measured prior to and at the 6–9-month follow-up were included in the analysis. Changes in A1C, body weight, and TDD insulin at time of follow-up were obtained and grouped according to treatment with U500 alone or in combination with RAI (U100) or LAI (U100) with or without oral agents.

Differences in clinical measures were analyzed using paired t tests. The relationship between reductions in A1C and use of LAI, RAI, or oral diabetes medications in combination with U500 was evaluated using logistic regression analysis. All statistical analyses were conducted using SPSS version 17 (SPSS Inc., Chicago, IL).

Results

Of more than 3,000 patients with type 2 diabetes, only 12 patients with clinical data available for review prior to and following initiation of U500 insulin were identified. Clinical characteristics of these 12 subjects are summarized in Table 1. The majority of patients received U500 as part of a BBI

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TABLE 1. CHARACTERISTICS IN SUBJECTS RECEIVING U-500 INSULIN ALONE OR AS PART OF BASAL/BOLUS INSULIN THERAPY

	<i>All patients</i>	<i>U500 + LAI</i>	<i>U500 + RAI</i>	<i>U500 alone</i>
<i>n</i>	12	7	3	2
Age (years)	54.4 (7.5)	55.7 (6.8)	53.7 (12.9)	51 (5.7)
Gender [<i>n</i> (%) men]	7 (58)	5 (71)	1 (33)	1 (50)
Diabetes duration (years)	13.8 (11.7)	12 (6.9)	15.7 (20)	18 (3.5)
A1C (%)				
Baseline	9.5 (1.1)	9.7 (1.1)	9.3 (1.6)	9.2 (0.14)
6–9-month follow-up	7.7 (1.0) ^a	7.9 (1.2) ^b	7.3 (0.8)	7.5 (0.9)
Weight (kg)				
Baseline	128.8 (32.7)	128.1 (34.5)	118.2 (55)	141.4 (3.9)
6–9-month follow-up	131.5 (31.3) ^c	129.8 (34)	126.5 (31.4)	144.8 (8.7)
BMI (kg/m ²)				
Baseline	43.3 (8.7)	43.3 (9.4)	41.1 (11.3)	46.5 (5.7)
Outcome	44.1 (8.7)	43.4 (9.1)	42.8 (10.7)	48.2 (8.1)
Total daily dose of insulin (units)				
Baseline	260 (111)	285 (104)	195 (143)	267 (111)
6–9-month follow-up	333 (106) ^d	363 (121) ^e	285 (102)	300 (0)
Number (%) of patients using oral diabetes agents				
Metformin	5 (42)	4 (57)	0	1 (50)
Pioglitazone	2 (17)	1 (14)	1 (33)	0

Data are reported as mean (SD) values, unless otherwise stated.

Significant differences between baseline and the 6–9-month time point: ^a*P* < 0.0001, ^b*P* = 0.004, ^c*P* = 0.014, ^d*P* = 0.002, ^e*P* = 0.013.

A1C, hemoglobin A1c; BMI, body mass index; LAI, long-acting insulin; RAI, rapid-acting insulin; U500, U-500 insulin.

regimen in combination with RAI (*n* = 3) or LAI (insulin glargine or NPH) (*n* = 7). Only two patients used U500 as their only insulin preparation. Four of seven patients receiving U500 with LAI and one receiving U500 alone were taking metformin. One patient receiving U500 alone and one with LAI were taking pioglitazone.

An overall 19% decrease in A1C was observed following initiation of U500, with a consistent trend in all subgroups (Table 1). Logistic regression analysis revealed no association between concurrent use of LAI, RAI, or oral diabetes medications with changes in A1C. These improvements in A1C were accompanied by an average weight gain of 3.3 ± 3.7 kg and a mean increase in TDD of 73 ± 60 units (Table 1). Based on body weight, the mean TDD increased from 2.0 to 2.5 units/kg/day following initiation of U500. Among patients using U500 in combination therapy, LAI accounted for 38% (131 ± 75 units) and RAI for 53% (180 ± 42 units) of the TDD, respectively.

Conclusions

We report that overall use of U500 is uncommon in this diabetes specialty clinic. When prescribed, U500 was most frequently administered as a component of BBI with either LAI or RAI. To our knowledge, this is the first report of U500 in combination with basal insulin preparations. The use of U500 in combination with RAI has been previously reported but not widely implemented in clinical practice.¹ Patients receiving LAI with U500 had slightly higher baseline A1C and TDD insulin than other subgroups, which may have influenced the decision to use this combination. The observed improvements with U500 in this study were similar among the three subgroups of patients, suggesting that combination therapy with LAI or RAI did not affect the improvement in glycemic control.

Similar to prior reports on clinical experience with U500, we observed improvements in A1C that were accompanied by weight gain. This weight gain has previously been attributed to increases in TDD with initiation of U500.^{7–9} Increases in TDD observed in this and prior reports runs counter to the clinical expectation that administering similar insulin doses at reduced volume would allow reductions in insulin requirements.^{3,6}

Severe insulin resistance has been defined as the requirement for >200 units of insulin/day.^{1,4,7,8,10} The average insulin dose in patients in this report was 2.5 units/kg/day, similar to what has been reported in prior studies of U500 (range, 1.5–3.6 units/kg/day).^{7,8}

There are several limitations of this study. The most important is the small number of subjects, suggesting that U500 is used infrequently and may in fact be underutilized. We searched a database of over 3,000 patients to identify 12 patients for this report. Information regarding frequency of hypoglycemia was not collected and would be useful in determining the safety of U500 as part of BBI therapy.

In summary, this investigation demonstrates variability with how U500 is prescribed in the clinical setting. We found that patients receive U500 insulin alone, in combination with LAI or RAI preparations, or with oral agents. This supports the need for more study of this preparation as monotherapy or as part of a basal/bolus regimen with LAI or RAI to better define its optimal use.

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Author Disclosure Statement

No competing financial interests exist.

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