Development and Implementation of a U-500 Regular Insulin Program in a Federally Qualified Health Center

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According to the 2014 National Diabetes Statistics Report (1), 29.1 million people in the United States (9.3% of the population) have diabetes; 28.7% of adults >18 years of age use insulin alone or in combination with oral medications (1). Nearly 35% of U.S. adults are obese, and this rate has steadily increased during the past 20 years (2). With the growing number of adults with diabetes and increasing rates of obesity, there is an increased prevalence of insulin resistance and thus a need for large daily doses of insulin for glycemic control.

U-500 regular (U-500R) insulin has been used for decades but has gained popularity in the past 10 years as a result of the increase in obesity and insulin resistance. The potency of U-500R insulin is five times greater than U-100 insulins; 1 mL of U-500R contains 500 units of insulin compared to 1 mL of standard U-100 insulin, which contains 100 units. The concentrated U-500R is advantageous for patients who are severely insulin resistant, requiring large doses of U-100 insulin because altered insulin absorption and leakage can occur when large volumes are injected, which reduces efficacy (3,4). To enhance U-100 insulin efficacy, practitioners often split the dose when the volume exceeds 40–60 units per dose. However, from the patient perspective, needing two injections to administer a single dose may be undesirable. For this reason, converting a patient requiring high doses of insulin from U-100 to U-500R could be considered because this option would decrease volume by 80% while still delivering the required number of units.

The pharmacokinetic characteristics of U-500R appear to fall between those of NPH insulin and U-100 regular insulin and allow U-500R to provide both basal and mealtime insulin coverage (5). Because of its pharmacokinetic properties, delayed peak effect, and prolonged duration of action, U-500R can be dosed twice daily (6). The dual basal and mealtime coverage provides an advantage, especially when patients require high doses of basal insulin in addition to mealtime insulin.

The use of U-500R can reduce the volume and number of insulin doses required. For example, a patient who requires 90 units of basal insulin twice daily and 30 units of rapid-acting or regular insulin three times daily with each meal would be injecting five doses of insulin daily. To enhance the absorption, the basal insulin dose may be divided into two doses of 45 units, but this would increase the number of daily injections to seven. The injection burden may result in patient nonadherence. Furthermore, adherence may be negatively affected by cost; the scenario outlined above would require six vials of basal U-100 insulin, two vials of U-100 rapid-acting or regular insulin, and two 100-count boxes of syringes each month. If the patient were transitioned to U-500R, in most cases,

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only two daily injections would be required, which would replace the numerous basal and mealtime insulin injections needed with U-100 insulin. Fewer daily injections can also reduce patient discomfort and lower the likelihood of developing lipodystrophy.

Although use of U-500R insulin has advantages, it is not without challenges. The two biggest challenges are weight gain and hypoglycemic events. Weight gain may occur if patient adherence to dietary and physical activity is not maintained. In one meta-analysis (7), the average amount of weight gain was 4.38 kg, although most patients' weight appears to stabilize within 6 months after initiation of U-500R insulin. In one study (8), weight increased by 3.2% at 3 months and by 1.6% at 12 months in patients who initiated U-500R insulin. These results were similar to a study by Lowery et al. (9), in which a 2% weight gain was observed with U-500R insulin (9).

The risk for hypoglycemic episodes is also intensified with the use of U-500R insulin because of its increased potency, decreased potential for leakage, and improved absorption. Based on a meta-analysis (9), severe hypoglycemia was not reported to be a problem and occurred at similar rates to U-100 regular insulin. However, Dailey and Tannock (5) noted that mild hypoglycemia increased slightly during the first few months, but then typically declined thereafter. The risk of hypoglycemia from U-500R insulin is especially concerning in patients who are nonadherent to provider instructions and who self-adjust their insulin independently.

Dosing errors are an additional challenge. According to the U.S. Food and Drug Administration (FDA), the majority of errors with U-500R insulin occur during prescribing, dosing, or administration (10). The FDA recommends that a conversion chart should always be used when administering doses from a U-500R vial with a U-100 insulin syringe or 1-mL tuberculin syringe if specific U-500R syringes are not available. The prescribed dose of U-500R insulin should always be expressed in actual units of U-500R, along with corresponding markings on the syringe the patient is using. This is because calculating the dose of U-500R can be confusing to some practitioners because dosing requires conversion to volume. Similarly, because patients on insulin are used to administering doses in units and not in milliliters, drawing up an accurate dose of U-500R can be confusing. In either situation, a dosing or dispensing error could result in a fivefold unintentional overdose or underdose, and a fivefold overdose could be fatal (11).

To address the issue of dosing errors, two new developments have emerged. A U-500–specific insulin syringe has been designed by Becton Dickinson and approved by the FDA with commercial availability in November 2016. The new syringe is 0.5 mL with bold U-500 markings in 5-unit increments and allows for dosing up to 250 units. It has a 6 mL × 31 gauge needle, which is the shortest insulin syringe needle available and is designed to minimize the risk of intramuscular injection (12). In 2016, the FDA approved the U-500R KwikPen by Eli Lilly. This pen dials and doses U-500R insulin up to 300 units per dose and eliminates conversion and dosing errors (13). The pen is convenient and easy to use but may be cost-prohibitive, especially for underserved populations who are uninsured or on government health care programs.

To enhance the safe and appropriate use of U-500R insulin in the outpatient clinical setting, a dosing protocol and a patient-provider U-500R insulin agreement should be considered. Here, we introduce a U-500R Insulin Program that includes a dosing and titration protocol, as well as an agreement between patient and providers at a federally qualified health center (FQHC).

Methods

Sheridan Health Services, an FQHC affiliated with the University of Colorado College of Nursing in Aurora, serves as a clinical faculty practice site and placement site for a variety of health care professional students. The clinic provides primary care, including women's health, dental care, behavioral health, and clinical pharmacy services in an integrated, interprofessional care model. The clinic provides access to a formulary of prescription and nonprescription drugs, including insulin, for uninsured patients. More than half of all patients (54%) are insured through Medicaid, and >27% prefer to communicate in Spanish.

Development of the U-500R Insulin Program

The U-500R Insulin Program was developed and initiated for appropriate patients requiring >200 units/day of insulin. Patients who were adherent with medications and clinic visits, had no or minimal cognitive impairment, were able to recognize hypoglycemia, and were willing to have weekly face-to-face or phone consultations with clinical pharmacy services were eligible for the program. It is crucial for patients on insulin, and especially U-500R insulin, to continue healthy lifestyle behaviors such as being physically active and making healthy meal choices; understand the risk, prevention, and treatment of hypoglycemia; and adhere to their doses without self-adjustment.

At the time the program was initiated, the clinical pharmacist, certified diabetes educator (CDE), and clinic providers collaboratively developed a U-500R insulin dosing protocol. This protocol was designed to provide a process for converting patients from U-100 to U-500R insulin and titrating doses of U-500R insulin (Table 1). After implementation of the U-500R protocol, it became apparent that safety can be compromised when patients do not adhere to follow-up visits or dietary and

TABLE 1. Sheridan Health Services' U-500R Insulin Management Protocol

Purpose: To establish an insulin titration and tracking process for patients with diabetes receiving insulin.

I. People responsible:

The clinical pharmacist will provide oversight of the processes described in this protocol. Student pharmacists will be directly involved in managing individual patients enrolled in the Insulin Management Program as described below.

II. Timeline for initiation:

October 16, 2014

III. Timeline for evaluation:

Every 6 weeks with the start of a new student who will be managing patients enrolled in the insulin management program.

IV. Practices:

a. For patients who are requiring high doses of U-100 insulin (e.g., >200 units per day), using U-500 should be considered if the patient is:
   i. Adherent with medications and follow-up visits
   ii. Has no or minimal cognitive impairment
   iii. Is able to describe signs/symptoms consistent with hypoglycemia
   iv. Is willing to have in-person or phone consultations weekly with student/pharmacist or provider

b. For patients referred to the U-500 Insulin Management Program, during the first visit, the student, pharmacist, or practitioner will:
   i. Determine total daily dose of U-500 by adding up the current total daily dose of U-100 insulin, dropping the U-100 dose by 20% and then dividing by 5 (U-500 is equivalent to 500 units/mL, and all other insulins are U-100, equivalent to 100 units/mL)
   ii. Determine the frequency of the U-500 based on the total daily dose of U-100
      1. 200–300 units/day of U-100 = BID dosing (60/40 with 60% of total daily dose before breakfast and 40% before dinner)
      2. 300–750 units/day of U-100 = TID dosing (40/30/30 with 40% of total daily dose before breakfast, 30% before lunch, and 30% before dinner)
   iii. Assess how patient manages hypoglycemia and review or provide the Rule of 15 hypoglycemia management education
   iv. Assess the level of physical activity since the last visit, provide education regarding benefits of physical activity, and have patient set personal physical activity goals
   v. Assess current diet, determine whether patient is willing to eat a bedtime snack if needed, provide education regarding diet, and have patient set personal dietary goals
   vi. Educate the patient that all other insulins will need to be discontinued with the initiation of U-500
   vii. Educate the patient that he or she will need to check and record a fasting blood glucose every morning, a 2-hour postprandial blood glucose every day (rotate among breakfast, lunch, and dinner), and a bedtime blood glucose every night
   viii. Provide 0.5-cc syringes to patient if patient only has 1-cc syringes at home and explain the importance of using the 0.5-cc syringes; have patient demonstrate how much insulin will be drawn up to ensure understanding and proper dosing
   ix. Verify that patient understands the U-500 dosing by having him or her tell you how many units will be administered with each dose, what s/he will do with the other insulins (discontinue use), and how s/he plans to manage hypoglycemic episodes and describe personal goals regarding physical activity and diet for the next week

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TABLE 1. Sheridan Health Services' U-500R Insulin Management Protocol, *continued from p. 164*

c. During subsequent visits, the student, pharmacist, or practitioner will:
   i. Obtain the blood glucose values for fasting, 2-hour postbreakfast, 2-hour postlunch, 2-hour postdinner, and bedtime
   ii. Determine U-500 dose adjustment:
      1. Divide 1,650 by total daily basal insulin dose to determine insulin resistance (or the blood glucose drop associated with 1 unit of insulin)
      2. Calculate the number of units required to achieve postprandial blood glucose of 180 mg/dL after the most problematic meal based on insulin resistance (calculated above) to estimate likely future insulin needs
      3. If postprandial blood glucose averages are >180 mg/dL, consider adding 0.1–0.2 mL of U-500 in the morning based on expected glucose reduction per the insulin resistance calculation
      4. If fasting glucose is >130 mg/dL and bedtime glucose is >150 mg/dL, consider increasing dose of bedtime U-500 by 0.1 mL and ensure that patient is taking a bedtime snack
   iii. Assess whether patient had any hypoglycemic episodes and review the rule of 15 hypoglycemia management education
   iv. Assess the level of physical activity since the last visit, provide encouragement so patient continues to engage in physical activity, and have patient set personal physical activity goals for the next week
   v. Assess current diet, determine whether patient has been eating a bedtime snack, provide encouragement so patient continues to engage in good dietary habits, and have patient set personal dietary goals for the next week
   vi. Reinforce that the patient will need to continue to check and record a fasting blood glucose every morning and a 2-hour postprandial blood glucose every day (rotate among breakfast, lunch, and dinner) and a bedtime blood glucose every night
   vii. The student will document all above information as a note in the electronic health record; include glucose readings, average numbers, treatment changes, and education provided
   viii. Weekly patient follow-up visits will continue as described above until patient's glucose is controlled with a fasting blood glucose <130 mg/dL and postprandial blood glucose <180 mg/dL
   ix. When all blood glucose levels are controlled, maintain the current dose until the next visit, stop weekly follow-up visits with the student or practitioner, and instruct patient to follow up with primary care provider

d. Hypoglycemia management:
   i. Appropriate hypoglycemia management includes the Rule of 15:
      1. If patient feels bad, s/he should check blood glucose level
      2. If <70 mg/dL, s/he should eat 15 g of fast-acting carbohydrates (e.g., 4 oz fruit juice, 1/2 can regular soft drink, 4 glucose tabs, or 4 hard candies), wait 15 minutes, and recheck blood glucose; if still low, repeat 15 g of fast-acting carbohydrates and check blood glucose in another 15 minutes
      3. Patients should continue checking blood glucose and eating 15 g of carbohydrates until blood glucose is >70 mg/dL, and then eat a protein-rich meal
      4. If blood glucose continues to stay low despite appropriate management, seek emergency medical care
   ii. If patient is having ≥2 hypoglycemia episodes within 1 week or ≥4 episodes within 1 month, discuss with clinical pharmacist or primary care provider

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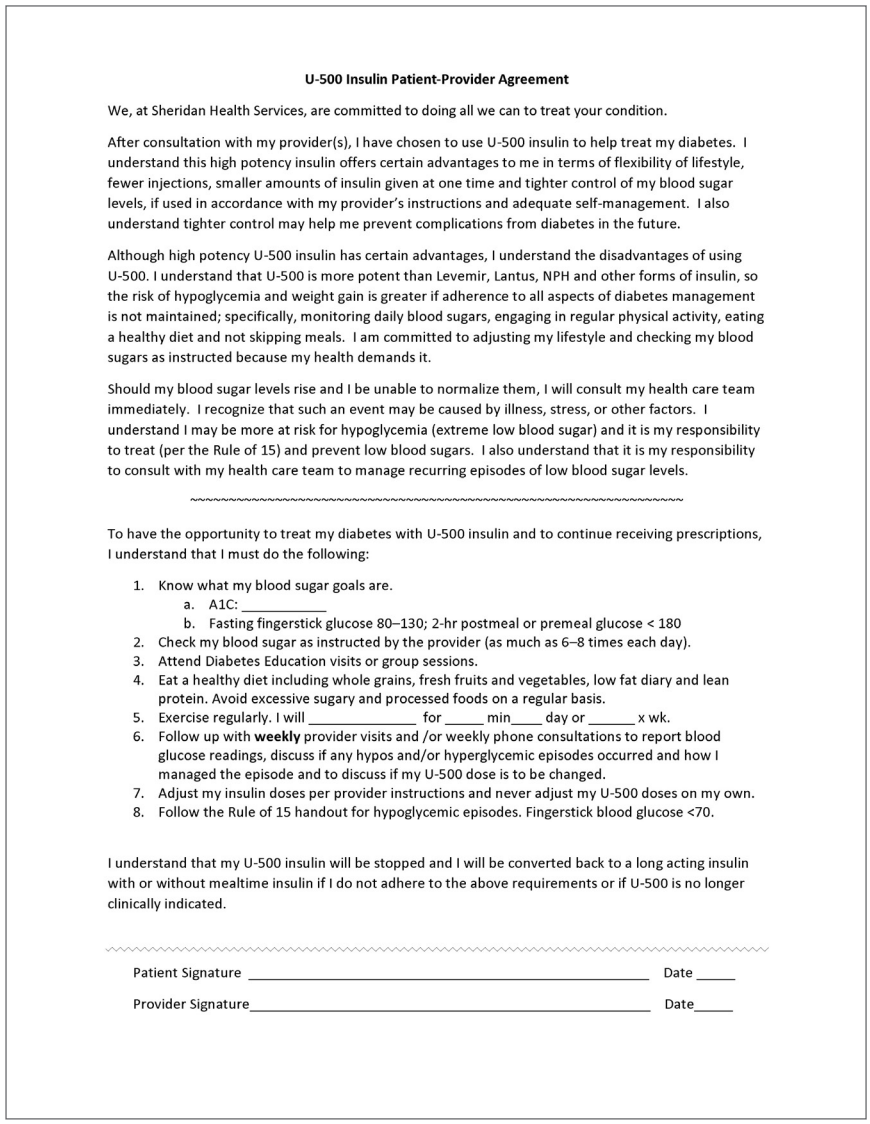
exercise regimens. For this reason, a patient-provider agreement was developed by the clinical pharmacist and CDE. This agreement was designed to encourage patient adherence with medications and prescribed regimens for monitoring, diet, exercise, and clinic visits to ensure overall patient safety (Figure 1). The document was



U-500 Insulin Patient-Provider Agreement

We, at Sheridan Health Services, are committed to doing all we can to treat your condition.

After consultation with my provider(s), I have chosen to use U-500 insulin to help treat my diabetes. I understand this high potency insulin offers certain advantages to me in terms of flexibility of lifestyle, fewer injections, smaller amounts of insulin given at one time and tighter control of my blood sugar levels, if used in accordance with my provider's instructions and adequate self-management. I also understand tighter control may help me prevent complications from diabetes in the future.

Although high potency U-500 insulin has certain advantages, I understand the disadvantages of using U-500. I understand that U-500 is more potent than Levemir, Lantus, NPH and other forms of insulin, so the risk of hypoglycemia and weight gain is greater if adherence to all aspects of diabetes management is not maintained; specifically, monitoring daily blood sugars, engaging in regular physical activity, eating a healthy diet and not skipping meals. I am committed to adjusting my lifestyle and checking my blood sugars as instructed because my health demands it.

Should my blood sugar levels rise and I be unable to normalize them, I will consult my health care team immediately. I recognize that such an event may be caused by illness, stress, or other factors. I understand I may be more at risk for hypoglycemia (extreme low blood sugar) and it is my responsibility to treat (per the Rule of 15) and prevent low blood sugars. I also understand that it is my responsibility to consult with my health care team to manage recurring episodes of low blood sugar levels.

To have the opportunity to treat my diabetes with U-500 insulin and to continue receiving prescriptions, I understand that I must do the following:

1. Know what my blood sugar goals are.
   a. A1C: _____
   b. Fasting fingerstick glucose 80–130; 2-hr postmeal or premeal glucose < 180
2. Check my blood sugar as instructed by the provider (as much as 6–8 times each day).
3. Attend Diabetes Education visits or group sessions.
4. Eat a healthy diet including whole grains, fresh fruits and vegetables, low fat diary and lean protein. Avoid excessive sugary and processed foods on a regular basis.
5. Exercise regularly. I will _____ for _____ min____ day or _____ x wk.
6. Follow up with **weekly** provider visits and /or weekly phone consultations to report blood glucose readings, discuss if any hypos and/or hyperglycemic episodes occurred and how I managed the episode and to discuss if my U-500 dose is to be changed.
7. Adjust my insulin doses per provider instructions and never adjust my U-500 doses on my own.
8. Follow the Rule of 15 handout for hypoglycemic episodes. Fingerstick blood glucose <70.

I understand that my U-500 insulin will be stopped and I will be converted back to a long acting insulin with or without mealtime insulin if I do not adhere to the above requirements or if U-500 is no longer clinically indicated.

Patient Signature _____ Date _____

Provider Signature_____ Date_____

FIGURE 1. Sheridan Health Services U-500 insulin patient-provider agreement.

reviewed by the providers to obtain input before implementation.

Process for Transitioning Patients From U-100 to U-500R Insulin

During patients' first visit, a patient assessment is completed and documented. The visit includes conversion of U-100 insulin to U-500R insulin, assessment of the patient's ability to identify hypoglycemic events, discussion of hypoglycemia management, reinforcement of the importance of blood glucose monitoring/scheduling, and assessment of current dietary habits and level of physical activity. Patients are educated about the expectations of enrollment into the program and asked to sign the patient-provider U-500R insulin agreement. After patients agree to adhere to expectations in the program, the U-500R insulin protocol is initiated, and U-100 insulins are discontinued. Then patient understanding is verified, and SMART (Specific, Measureable, Actionable, Attainable, Realistic, Timely, and Time-Bound) goals are established. The patient must demonstrate the proper process for drawing up the accurate amount of U-500R insulin, accurately describe when blood glucose testing will occur, and accurately describe how hypoglycemia will be managed should it occur. Patients must agree to weekly follow-up via phone or face-to-face visits.

Subsequent visits or phone calls with patients occur every 1–2 weeks and focus on reviewing the items discussed at the first visit and titrating insulin per protocol, as indicated by average blood glucose values. If there is deviation from or evidence of nonadherence to the expectations outlined in the patient-provider agreement, the agreement is reviewed. At this time, patients are notified that, if they do not abide by the agreement, their U-500R insulin will be discontinued, and they will be transitioned back to U-100 insulins.

Results

Three case examples illustrate the benefit of the U-500R Insulin Program, which incorporated the use of an insulin dosing and titration protocol and a patient-provider agreement. All three cases involved patients with diabetes who required large doses of insulin. Of the three patients switched to U-500R insulin, all had improved glycemic control. One, whose A1C goal was 8% due to age and comorbidities, had an A1C reduction from 9.2 to 6.9%, which resulted in a reduction of the U-500R insulin dose. The other two patients each had an A1C goal of 7%; one had a reduction from 10.4 to 8.1%, and the other had a reduction from 10.5 to 7.8% before being titrated off of U-500R insulin and transitioned back to U-100 in advance of a scheduled bariatric surgery procedure. All three patients had significant weight gain of 3–6% after initiating U-500R insulin, with an average 10-lb weight gain within the first 2 months after starting U-500R insulin. However, with the initiation of the patient-provider agreement, patients' weight stabilized within 3–4 months. One patient had hypoglycemic events on an ongoing basis, primarily due to lifestyle and eating habits. Both issues demonstrate the

importance of frequent and consistent communication with patients on U-500R insulin, patient adherence to lifestyle modification, and the development of patient-centered goals for diabetes care.

Development of a specialized protocol and patient agreement was an effective strategy for managing complex patients when using a collaborative approach to expand the scope of primary care to a role traditionally carried out by specialty care.

Discussion

The U-500R Insulin Program was developed for the few patients who were severely insulin resistant and whose diabetes was not controlled on large doses of U-100 insulin. Initially, only the U-500R insulin dosing protocol was developed and implemented. The protocol was successful in decreasing patients' blood glucose values and A1C compared to U-100 insulins. On average, A1C decreased by 2.3–2.7%, with an average reduction of 2.4% after conversion from U-100 insulins to U-500R insulin. This A1C reduction observed with this program was more than what has been demonstrated in the literature. In a study by Eby et al. (14), it was reported that mean A1C in 445 patients on U-500R insulin decreased by 0.68% (P <0.0001 compared with baseline A1C) (14).

Furthermore, the patients in this program experienced more weight gain than what was expected. The three example patients who were converted to U-500R gained an additional 3–6% body weight, which was similar to the weight gain observed in previous studies (7–9). Based on patient visit data, it was identified that adherence to diet and exercise was lacking, and this was thought to have contributed to patients' weight gain.

The study by Eby et al. (14) also noted that the proportion of patients having hypoglycemic events, captured primarily in outpatient settings, increased from 6.7 to 11.9% (P <0.0001). Eby et al. reported that these events also increased from 0.23 to 0.39 incidents per patient per year, which was an increase of 0.13% (P = 0.003). Although the patient in one of our example cases described above was experiencing hypoglycemic episodes, it was determined that he was not eating regularly or adhering to his prescribed schedule for meal timing.

Conclusion

The implementation of a U-500R Insulin Program that included an insulin dosing and titration protocol and a patient-provider agreement helped to ensure the safe and effective use of U-500R insulin in a small sample of patients in an FQHC. The protocol aided the safe initiation and appropriate titration of U-500R insulin. With the use of U-500R insulin, all patients in the program demonstrated an improvement in diabetes control, as indicated by reductions in A1C. Although weight gain and hypoglycemia occurred, they were diminished after implementation of a patient-provider agreement.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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