

Don't Resist Using U-500 Insulin and Pramlintide for Severe Insulin Resistance

Virginia Valentine, CNS, BC-ADM, CDE, FAADE

We have all had that patient: you keep increasing the insulin doses, and now they add up to > 200 units/day. And yet, blood glucose levels are still beyond the goal range. The patient says, "Maybe insulin doesn't work for me," and you and the patient both feel hopeless and helpless.

It is important to help such patients understand that it is not their fault. Insulin resistance is frustrating for both patients and health care professionals (HCPs) and requires a multipronged approach: first, finding the right combination of medications to manage the glucose levels, and, second, addressing lifestyle issues that can help reduce insulin resistance.

This is the time to consider using U-500 regular insulin. U-500 is an insulin formulation that is five times more concentrated than usual U-100 insulin. Made by Eli Lilly, it is the only concentrated insulin currently available in the United States.

Potential Advantages of U-500 Insulin

Concentrated U-500 insulin allows people who require very high doses of insulin to get their doses in a lower volume. For example, a patient who is taking 100 units of U-100 insulin would take an injection with a 20-unit volume of U-500 insulin.

U-500 is a human regular insulin, but its time action is not the same as the usual U-100 formulation. It has the same peak as U-100 regular insulin, but its duration is more like

that of NPH insulin, ~ 12 hours. Given these characteristics, U-500 works as both basal and prandial (bolus) insulin, so patients who use it not only take less insulin by volume, but also typically need only one type of insulin.

Another major difference is the cost. Although patients may be shocked to learn that the cost of a 20-ml vial (twice the amount of a usual 10-ml vial) is ~ \$500, it is actually equivalent unit for unit to the cost of U-100 human insulin because 20 ml of U-500 provides the same coverage as 10 vials of U-100. And, U-500 insulin costs only about half as much as the newer analog insulins. This can be a significant savings for patients who may be charged insurance co-payments by the vial instead of a single co-payment for a month's supply of insulin.

U-500 insulin has been available since the 1950s, but its use has been increasing dramatically in recent years, in part because of the increase in type 2 diabetes and obesity, which increases insulin resistance. For patients who are approaching or exceeding 200 units/day of insulin, U-500 may be a welcome solution. For many HCPs, U-500 insulin is an intriguing, but sometimes mysterious option. This article offers a simple process for starting and fine-tuning a U-500 insulin regimen.

Patient Education Is Crucial

Patient education is the most important aspect of successfully using

U-500 insulin. Many HCPs are apprehensive about prescribing U-500 insulin because of its concentration and related potential for dosing errors and because HCPs who are not diabetes specialists may be unfamiliar with or unclear about its use and how best to prescribe it. For this reason, it is crucial for patients to understand the insulin and how it differs from other insulin formulations. Typically, patients adjust rapidly to using U-500 insulin, but there remains a great deal of confusion about it in pharmacies and on inpatient hospital units.

Figure 1 offers a teaching tool for patients who are starting on U-500 insulin and can be photocopied and distributed to help ensure that patients have correct information about this product in writing. Patients should be instructed about both the action of U-500 insulin and the correct way to measure doses.

Most patients prefer using U-100 syringes because of the availability of finer and shorter needles and because they are already familiar with these syringes. The author's practice recommends that patients use U-100 syringes in the smallest size appropriate for their insulin dose. In other words, if patients are taking < 30 syringe units or 30 unit markings on a U-100 syringe of U-500 at any dose (150 actual units), a U-100 syringe that has maximum dose of 0.30 ml or 30 units is the best choice and limits the risk of giving too much insulin. If patients are taking up to 50 syringe units of U-500

(250 actual units), a 50-unit syringe can be used. If a tuberculin syringe is used to measure volume of insulin, that type of syringe holds 1 ml, or 500 units of U-500. Figure 1 shows patients how volume-measure and U-100 syringe markings compare.

Converting a Standard Basal-Bolus Regimen to U-500

There are six steps to converting a basal-bolus insulin regimen to a regimen using U-500 insulin at breakfast, lunch, and dinner.

1. Add all daily basal and bolus doses to calculate the patient's total daily dose (TDD) of insulin.
2. Divide the TDD by 3 to establish doses to be given at each meal.
3. Divide each dose by 5 to determine the dose in "syringe marking units."
4. Consider lowering the lunchtime dose a bit and adding that amount to the dinner dose if dinner is the largest meal of the day.
5. Obtain patient's commitment to eat three meals daily and to check blood glucose levels before each meal and at bedtime.
6. Instruct patient on dosing and timing of insulin and hypoglycemia management using the teaching tool in Figure 1 or similar materials.

As an example, a patient who takes 80 units of glargine at 10:00 p.m. and 50 units of aspart before each meal has a TDD of 230 units of U-100 insulin. Dividing the TDD by 5 results in a TDD of 46 units of U-500 in a U-100 syringe. Dividing the U-500 TDD by 3 results in mealtime doses of 15 units of U-500 in a U-100 syringe.

As an alternative, the TDD of U-500 insulin can also be split as two injections: 60% at breakfast and 40% at dinner. A third injection can be added later at lunch and, if needed, a small injection can be added at bedtime.

Prescribing U-500 Insulin

Pharmacies can easily mistake a U-500 insulin prescription for a U-100 prescription, so it is important to reinforce with patients that their U-500 insulin is different and that they must check the insulin in the bag before they walk away from the pharmacy counter. U-500 insulin comes in 20-ml vials and has orange stripes on the box and label.

When writing the prescription, the author suggests writing "Humulin R U-500 [underline U-500 several times], 20 ml vial #1 vial, DAW [dispense as written]." This will alert the pharmacy staff that this is a prescription requiring special attention.

Dosing instructions should read, "Draw up XX unit markings on insulin syringe before each meal." There are 2,000 "syringe units" in the vial. If a patient is taking, for example, 18 "unit markings" or "syringe units" three times a day for a total of 54 syringe units/day, one vial will last at least 1 month. One vial will give patients about 60 "syringe units" each day for 1 month.

Reinforce with patients that every unit of U-500 is the same as 5 units of their usual insulin. They are accustomed to increasing their dose by 5 or 10 units if they are eating a large meal. If they want to increase their U-500 dose for a large meal, they should increase by 1 or 2 units.

Initiating and Adjusting U-500 Therapy

Patients should not take their first U-500 injection until at least 12–16 hours after their last dose of long-acting insulin. For many, this means their first U-500 dose will happen in the morning.

Most patients will find that their pharmacy needs to order U-500 insulin, so it may take a day or two to get their prescription filled.

Once they have started their new regimen and are checking their blood glucose levels 3–4 times daily, the following steps can be used to fine-tune their regimen:

- Step 1: Look for and address hypoglycemia events.
- Step 2: Fix the fasting glucose levels by adjusting the evening dose. (Some people will need to split their evening dose, taking half before supper and half at bedtime.)
- Step 3: Address postprandial glucose levels by adjusting the dose or timing of prandial doses (30–60 minutes before meals) or decreasing carbohydrate intake at meals.

Pramlintide: An Additional Strategy

One additional strategy that can be used with patients using U-500 insulin is to consider adding a dose of pramlintide with each meal. Pramlintide is an analog of amylin, a pancreatic β -cell hormone that, like insulin, is deficient in people with diabetes.

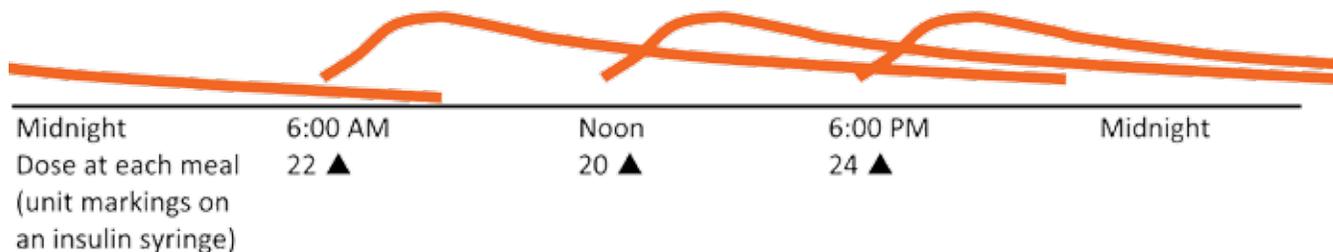
Pramlintide offers several benefits for people using U-500 insulin. Specifically, it:

- Slows stomach emptying so that glucose excursions from meals more closely match the peak of U-500 insulin, about 2–3 hours after injection,
- Suppresses glucagon and, therefore, hepatic glucose production after meals and, in turn, improves postmeal glucose levels, and
- Helps patients by increasing satiety so they are able to eat less, which can reduce weight gain or promote weight loss.

Pramlintide is available in pen injectors. For patients using U-500 insulin, start pramlintide with a 60- μ g dose and lower the U-500 dose by \sim 25% so patients can see how the pramlintide affects their appetite. This will enable them to eat less if they feel full faster without worry-

GETTING STARTED WITH U-500 INSULIN

- What is U-500 insulin?** It is insulin that is **5 times** more concentrated than your usual U-100 insulin (there are 500 units in 1 milliliter instead of the usual 100 units in 1 milliliter)
- Why do you need it?** For people who need large doses of insulin, U-500 helps you get the right dose without taking large volumes of insulin.
- How does it work?** U-500 insulin starts working the first hour after it is injected and lasts up to 12 hours.
- Example:** This is a typical dose schedule for U-500 insulin.



Your glucose goals: Fasting and before meals _____ 2 hours after meals _____ A1C _____

Check your blood glucose: Bring your logbook and meter to every visit. Times to check are marked below with ↓.

Eat and take your U-500 insulin at regular times. Your doses are listed below. Mealtimes are marked with ▲.

Figure 1. A teaching tool for patients using U-500 insulin. Permission is granted to reproduce this material for nonprofit education purposes. Written permission is required from the American Diabetes Association for all other purposes.

Getting the Correct Dose of U-500 Insulin

Your U-500 insulin comes in 20-milliliter vials (twice as much as in usual insulin vials). There are orange stripes on the box and label. Check your insulin before you leave the pharmacy to be sure you have the right insulin.



U-500 insulin is **5 times** more concentrated than usual U-100 insulin, so every unit of U-500 drawn on an insulin syringe is the same as 5 units of usual insulin. It is important to understand your dose and the amount you are drawing up in the syringe to be sure you get the right dose.

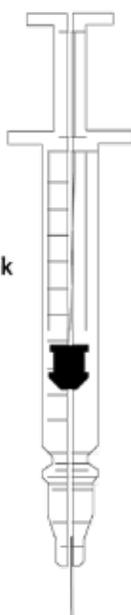
Type of syringe you will use: U-100 insulin syringe
 tuberculin syringe

Example: If your diabetes care team wants you to get 100 units of insulin, you will draw up to the 20-unit mark on an insulin syringe to get that amount of U-500 insulin (it is 5 times more concentrated).

Tuberculin syringe:

100 units of U-500
 = 20 units of U-100
 = 0.2 ml on the syringe

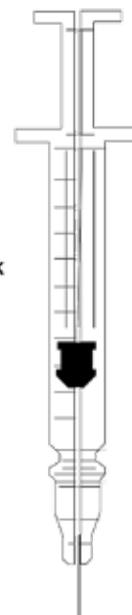
Your dose: ____ units
 Draw up to: ____ ml mark



U-100 insulin syringe:

100 units of U-500
 = 20 units of U-100

Your dose: ____ units
 Draw up to: ____ unit mark



Treating Low Blood Glucose (Hypoglycemia)

If you feel shaky, sweaty, weak, or nervous or have a headache, you might have low blood glucose. Check your blood glucose, if possible. If it is below 80 mg/dl, take one of the following treatments and then wait 15 minutes. Re-check your blood glucose. If it is not above 80 or you are not feeling better, repeat.

3 glucose tablets

1/2 cup of real soda pop (not sugar-free)

1 cup of milk

1/2 cup of juice

ing about hypoglycemia. After 3 days of taking pramlintide without experiencing nausea, increase the pramlintide dose to 120 μg and then begin increasing the insulin dose to achieve blood glucose targets. Pramlintide can be taken from 20 minutes to immediately before meals.

Continued Emphasis on Lifestyle Modification

Because weight gain is a common problem with insulin use in general and especially when improving control, it is important to continue working with people with insulin resistance on lifestyle modifications related to meal planning, portion control, and physical activity. Referring patients for medical nutritional therapy and other supports such as weight loss programs can be beneficial.

Summary

U-500 insulin can result in improve-

ment in glycemic control with reasonable dosing amounts so that patients do not have to take 2–3 injections to get the volume of insulin they need for a single dose. Adding pramlintide to a U-500 regimen can help patients improve their control while assisting them with hunger and weight issues. Most importantly, such a regimen can give hope to severely insulin-resistant patients who have had difficulty with diabetes control using conventional U-100 insulin products.

Suggested Readings

1. Brown A, Desai M, Taneja D, Tannock LR: Managing highly insulin-resistant diabetes mellitus: weight loss approaches and medical management. *Postgrad Med* 122:163–171, 2010
2. Hirsch IB: Intensifying insulin therapy in patients with type 2 diabetes mellitus. *Am J Med* 118 (Suppl. 5A):21S–26S, 2005
3. Lane WS, Cochran EK, Jackson JA, Scism-Bacon JL, Corey IB, Hirsch IB, Skyler JS: High-dose insulin therapy: is it time for U-500 insulin? *Endocr Pract* 15:71–79, 2009
4. Ratner RE, Want LL, Fineman MS, Velte MJ, Ruggles JA, Gottlieb A, Weyer C, Kolterman OG: Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther* 4:51–61, 2002

Virginia Valentine, CNS, BC-ADM, CDE, FAADE, is a clinical nurse specialist at the Diabetes Network at Northside Family Medicine in Albuquerque, N.M. She is a deputy editor of Clinical Diabetes.