

U-500 Insulin: When More With Less Yields Success

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Syndromes of severe insulin resistance were first reported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1976,¹ with either inherited insulin receptor abnormalities or the presence of autoantibodies to the insulin receptor. These patients were some of the first with severe insulin resistance who were treated with U-500 insulin first used clinically in 1952.^{2,3} Initially, patients requiring this concentrated insulin preparation were those with type 1 diabetes with high antibodies to insulin resulting from the use of animal-source insulin causing antibody formation. The introduction of sulfated insulin in the 1970s and the availability of human insulin preparations starting in the 1980s has shifted the use of U-500 insulin to patients with extreme forms of insulin resistance.^{1,2} With the prevalence of obesity and the growing epidemic of type 2 diabetes, the utility of U-500 insulin can be expanded from syndromic forms of insulin resistance to patients with type 2 diabetes who require > 200 units of insulin per day. However, these syndromic patients have taught us a great deal about how to administer and manage U-500 insulin in patients.

The American Diabetes Association (ADA) has four standard classifications of diabetes mellitus: 1) type 1 diabetes, 2) type 2 diabetes, 3) other specific types of diabetes, and 4) gestational diabetes.⁴ Regardless of the cause, the four classifications have one symptom in common: hyperglycemia. Chronic hyperglycemia from diabetes is associated with macrovascular and microvascular complications such as heart, kidney,

nerve, and eye disease. Several long-term diabetes complication trials (i.e., the Diabetes Control and Complications Trial, the Epidemiology of Diabetes Interventions and Complications Trial, the Action to Control Cardiovascular Risk study, and the Action in Diabetes and Vascular Disease study) provide the fundamentals for treating hyperglycemia as close to ADA targets (i.e., A1C < 7%) as possible.³⁻¹³

Figure 1 displays typical daily doses of insulin/kg of body weight/day according to type of diabetes. The bell-shaped curves represent the percentage of patients requiring various amounts of insulin/kg of body weight/day. The figure shows doses of insulin typical of each type of diabetes to achieve ADA-recommended target blood glucose levels (for type 1 diabetes, doses from 0.25 to 1 unit/kg/day; for type 2 diabetes, doses from 0.6 to 2.5 units/kg/day; and for other forms of insulin resistance, ≥ 2 units/kg/day). Given the epidemic of obesity and the fact that insulin is dosed per kg of body weight, patients requiring > 200 units of insulin/day are not unusual.

There is often a reluctance to use higher doses of insulin, because of concerns that hyperinsulinemia is atherogenic. However, higher doses of insulin may still be somewhat effective, and evidence-based medicine has shown that therapeutic goals are achievable through use of insulin therapy for $\geq 40\%$ of patients with diabetes.^{3,5-15} Treatment decisions should be guided by evidence-based medicine and the known benefits of treating patients to target levels of glycemia. Insulin doses should be increased as warranted to achieve

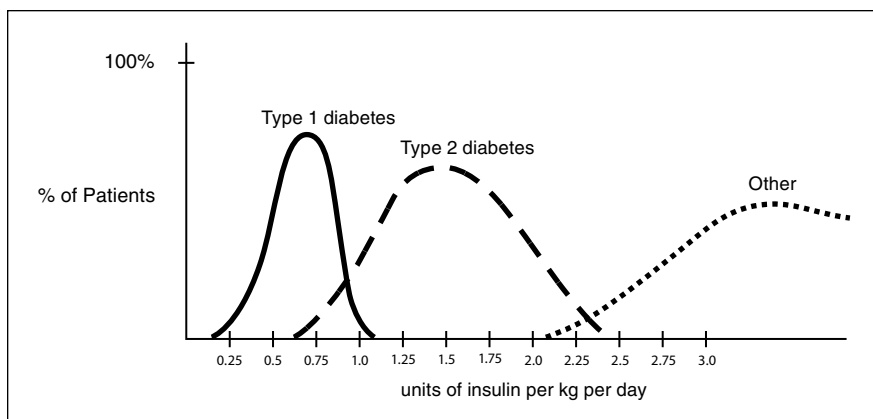


Figure 1. Practical diagram of typical insulin dose requirements for type 1, type 2, and other forms of diabetes mellitus. Typical insulin dose requirements for diabetic patients expressed as individual bell-shaped curves showing the percentage of patients at each TDD level. Representative dose ranges to achieve target goals are shown (i.e., 0.25–1 unit/kg of body weight/day for type 1 diabetes, 0.6–2.5 unit/kg of body weight/day for type 2 diabetes, and 3 to > 500 units/kg per day for syndromic insulin resistance). In type 2 diabetes and insulin resistance syndromes, the bell-shaped curves are broader, reflecting a broader dose range for target blood glucose levels. Indeed, the right side of the curve representing other forms of diabetes does not return to the horizontal axis because occasionally sufficient doses of insulin cannot be administered to alleviate hyperglycemia in some syndromic forms. The values for type 1 and type 2 diabetes are derived from the literature, and the values for the syndromic forms are taken from NIDDK experience.

glycemic control. When high insulin doses are required (e.g., > 200 units/day), a more concentrated insulin preparation such as U-500 insulin may be used^{3,15–19} and can address volume challenges that accompany higher doses.

Clinical Conditions for Use of U-500 Insulin

The principles of treating insulin-resistant patients to target levels of glycemia with larger doses of insulin also apply to the growing subset of obese patients with type 2 diabetes. To date, NIDDK has treated > 70 patients with U-500 insulin.^{1,2,15,16,20–25} Syndromic forms of insulin resistance, including type A and type B insulin resistance syndrome, congenital and acquired generalized lipodystrophy, hyperandrogenism/insulin resistance/acanthosis nigricans, and Rabson-Mendenhall syndrome afflict most of the patients, but some are severely insulin-resistant patients with type 2 diabetes.^{1,2,15,16,20–25}

Based on experience using U-500 insulin, a practical algorithm for administering U-500 insulin has

been developed (Table 1). This algorithm includes instructions for how to divide the total daily insulin dose throughout the day, how to account for the dose-response properties of U-500 insulin, and how to use U-500 insulin with an insulin pump.

Deciding to begin U-500 therapy

Patients who require > 200 units/day of U-100 insulin for more than three consecutive days may benefit from U-500 insulin. Patients whose insulin resistance is the result of steroid therapy that will not be decreased in the coming several weeks would also benefit from U-500 insulin, and making the switch would be practical.

Because doses of U-100 insulin > 200 units/day are cumbersome to administer, patients often find it difficult to adhere to such insulin regimen. It is therefore imperative to assess whether patients are actually following their prescribed regimen. Poor adherence may lead to unnecessary dose increases.

A delay in changing to U-500 may occur if prescribers are not familiar with using U-500 insulin and are concerned that U-500 is only

used for syndromic or other forms of insulin resistance. Although it is important to investigate all causes of insulin resistance, increasing the insulin dose to achieve glycemic targets should not be delayed. When determining the amount of U-500 insulin needed, the current verified U-100 total daily dose (TDD) is used to determine the U-500 TDD. Usually, patients are hyperglycemic on their current U-100 insulin, and improved insulin action from the decreased volume of U-500 insulin will make a 1:1 conversion a good starting point.

If the increasing need for higher doses of insulin is related to a patient's weight, the importance of diet, physical activity, and weight management must be stressed. In patients with type 2 diabetes related to obesity, even moderate weight loss can have a significant benefit on insulin resistance.²⁶ Facilitating the change from U-100 to U-500 insulin can be an opportunity to emphasize caloric control because the U-500 will only be managing the glycemia and the underlying reasons leading to diabetes must still be addressed.

Pharmacology and Availability of U-500 Insulin

Pharmacological profile

The human form of U-500 insulin has been available since 1997 and is the only stable marketed form of concentrated insulin today. It is only available in the form of regular insulin. The duration of action of insulin activity is regulated by the rate of insulin absorption after it is administered subcutaneously. Daily absorption rates of U-500 insulin seem to be consistent, regardless of injection site.^{3,15,17,27,28}

The available forms of insulin differ in their onset, peak, and duration of action and are often marked for their basal or bolus qualities. Regular U-100 insulin demonstrates a peak effect within 2–4 hours of administration and a 5- to 7-hour duration of action. U-500 insulin has an onset and peak of action similar to that of regular insulin but a duration of action of up to 24 hours.^{3,15–17,27,28} Duration of action is even more prolonged in patients

Table 1. Administration and Dosing of U-500 Insulin^{3,15}

TDD (units/day)	Injection Frequency/Delivery Schedule	Doses as a Percentage of TDD	Dosing Adjustments
200–299	Two injections per day (i.e., 8:00 a.m., 6:00 p.m.)	a.m. injection = 60% of TDD p.m. injection = 40% of TDD (i.e., 60/40)	For blood glucose levels < 50 mg/dl of target, make incremental increases and decreases every 5 units or 0.01 ml of U-500 per dose/bolus. For blood glucose levels > 50 mg/dl of target, make incremental increases and decreases every 10 units or 0.02 ml of U-500 per dose/bolus. For patients using an insulin pump, basal rates can have finer adjustments because of pumps' ability to infuse fractions of units.
	Three injections per day (i.e., 8:00 a.m., noon, 6:00 p.m.)	40/30/30, 45/35/20, or 40/40/20	
	Via insulin pump: 1 unit = 0.01 ml; 0.01 ml of U-500 insulin = 5 units	Three or four mealtime boluses. For basal rate that is 20% of TDD, boluses are 30/30/20 or 30/25/20/5. For basal rate that is 50% of TDD, boluses are 20/20/10 or 20/15/10/5. Bedtime snack bolus should be ≥ 10% of TDD.	
300–599	Three injections daily (i.e., 8:00 a.m., noon, 6:00 p.m.)	40/30/30, 45/35/20, or 40/40/20	For blood glucose levels within 100 mg/dl of target, make incremental increases and decreases every 25 units or 0.05 ml of U-500 per dose/bolus. For blood glucose levels > 100 mg/dl of target, make incremental increases and decreases every 50 units or 0.1 ml of U-500 per dose/bolus. For patients using an insulin pump, basal rates can have finer adjustments because of pumps' ability to infuse fractions of units.
	Four injections daily (i.e., 8:00 a.m., noon, 5:00 p.m., 10:00 p.m.)	30/30/30/10	
	Via insulin pump: 1 unit = 0.01 ml; 0.01 ml of U-500 insulin = 5 units	Same as above	
600	Four injections daily (i.e., 8:00 a.m., noon, 5:00 p.m., 10:00 p.m.) Do not inject more than 2 ml in any one injection site.	30/30/30/10	All incremental changes are every 50 units or 0.1 ml of U-500 per dose.

TDD, total daily insulin dose

with insulin receptor abnormalities because of insulin degradation impairment.

As doses of insulin increase, the volume being injected increases, which impairs the typical pharmacodynamic properties associated with different forms of U-100 insulin.^{3,15,17,27,28} Higher doses have the potential to postpone peak action and prolong duration of action. For example, an injection of 20 units of regular insulin has a significantly different time-action profile than an injection of 50 units.

The adverse reactions that have been reported for U-500 insulin are similar to those reported for U-100 insulin preparations. Hypoglycemia is one of the most frequent adverse events experienced by all patients taking insulin. Of particular note for users of U-500 insulin is that

secondary hypoglycemic reactions may develop 18–24 hours after injection.^{3,15–17} The risk posed by these secondary hypoglycemic reactions influences the dosing and administration schedule of U-500 insulin.

Cost and packaging of U-500 insulin

Although U-500 insulin is more expensive than other insulin on a per-milliliter basis, the actual volume of insulin used is decreased, resulting in a lower cost per unit of insulin than for other forms of insulin. Thus, cost savings may be one potential benefit of using U-500 insulin (Table 2).^{3,15,16,29} Moreover, the use of U-500 insulin requires fewer syringes or pump cartridges to administer lower volumes of insulin, which results in cost savings for diabetes care supplies.^{3,15,16,29}

In the United States, U-500 insulin is supplied in 20-ml vials. This concentrated form is differentiated from other forms of insulin by its larger vial size, diagonal orange stripes on the box, and vial labeling. U-500 is not available in insulin pens or pen cartridges; the manufacturer does not recommend administering U-500 via pen devices.

Most pharmacies and hospitals do not routinely stock this form of insulin; 1–2 business days may be required to obtain it. Outside of the United States, health care providers with patients who may benefit from this form of insulin should contact their Eli Lilly representative for assistance in obtaining this form of insulin via the proper channels and pharmaceutical sales rules of their country.

Table 2. Cost Analysis of Insulin^{14,15,29}

Insulin Type and Strength (units/ml)	Volume (ml)	Average Wholesale Price Per Vial* (U.S. dollars)	Price Per Unit* (U.S. dollars)
Regular insulin, 500	20	222.21	0.02
Regular insulin, 100	10	37.70	0.04
Insulin lispro, 100	10	87.89	0.09
Insulin aspart, 100	10	95.71	0.10
NPH insulin, 100	10	37.70	0.04
Insulin glargine, 100	10	84.20	0.08
Insulin detemir, 100	10	90.31	0.09

*As of September 1, 2007.

Dosing of U-500 insulin

The pharmacodynamic properties of U-500 insulin, which have features similar to both NPH and regular insulin, require that U-500 be dosed and scheduled differently than one would typically dose and schedule U-100 insulin. To facilitate use, dosing is divided into three major categories: one for those requiring 200–299 units of insulin per day, one for those requiring 300–600 units per day, and one for those requiring > 600 units per day (Table 1).

For those requiring 200–299 units/day. This dose range can be managed with multiple daily injections of U-500 insulin or the infusion of U-500 insulin via an insulin pump.

If twice-daily injections are the delivery method selected, 60% of the TDD should be injected in the morning and 40% in the evening. If injections three times per day are preferred, again the higher percentage of the TDD should be given for breakfast and lunch, and the lower percentage at dinner.

If an insulin pump is selected, basal rates tend to be set higher during the day and lower at night. Frequent changes in basal rates should be avoided because the pharmacokinetics of U-500 insulin may cause a delayed effect. The set times of the basal rate should be programmed 1–2 hours before the actual time of the desired effect. For example, if a typical basal rate was from 6:00 a.m. to 6:00 p.m. with U-100 rapid-acting insulin in the pump, that same basal rate should be set for 5:00 a.m. to

5:00 p.m. with U-500 because of the delay in dose effect.

Bolus doses should be programmed into the pump in the amounts recommended above for injection three times daily before meals; insulin sensitivity factors for correction doses and carbohydrate ratios for matching bolus insulin to nutrient intake should be entered manually or a set basal regimen should be programmed. Patients using pumps should be instructed to not administer a bolus dose more frequently than every 4–6 hours because this leads to “insulin stacking” (when the effect of an insulin dose overlaps the remaining effects of the previous dose). Insulin pumps are programmed to take “insulin on board” (the remaining active portion of a previous insulin dose) into account to prevent insulin stacking when using rapid-acting insulin products.

Lane et al.^{3,30} reported detailed instructions on the use of U-500 in an insulin pump and an explanation of how parameters should be entered in a pump when initiating therapy. Lane’s U-500 insulin guidelines and algorithms have been used for insulin pump regimens using between 100 and 200 units/day.³

For those requiring 300–599 units/day. U-500 insulin injections three to four times daily or insulin pump use for this dose range are recommended. The doses can be divided as 40–45% in the morning, 30–40% for lunch, and 20–30% for dinner. The decision to add bolus insulin (e.g., three to four injections)

to basal dosing is usually indicated when blood glucose levels are consistently elevated in the morning. For four daily injections, higher doses during the daytime and a lower dose at bedtime (i.e., 30% of the TDD with each meal and 10% at bedtime) is recommended. Still, twice-daily dosing may be used; Ballani et al.^{15,18} reported satisfactory use of twice-daily dosing for TDDs ≤ 650 units.

For those requiring 600 units/day. We recommend U-500 insulin injection four times daily exclusively for doses > 600 units/day. Doses may be divided evenly, but if nocturnal or morning hypoglycemia is present, we recommend that the bedtime dose be reduced. TDDs ≥ 2,000 units/day, may necessitate the use of 3-ml syringes with a 27-to 30-gauge needle added, which will enable injecting more than 1 ml, while taking care not to inject more than 2 ml, insulin at a time.^{3,15} Insulin pump therapy is not recommended for patients whose insulin requirements are > 600 units/day because the large volume injected at the catheter site would impair the absorption of U-500 insulin. Using multiple daily injections will allow the volume of U-500 injected to be distributed more evenly and improve the dose-responsiveness of the U-500 at these ranges.

Dose adjustments. Typically, patients calculate insulin doses at each meal based on their standard bolus (which can be fixed or calculated using an insulin-to-carbohydrate ratio), plus any needed correction insulin based on their premeal blood glucose level. When using U-500 insulin, insulin sensitivity factors for correction doses and insulin-to-carbohydrate ratios for nutrient coverage are too sensitive for the severe insulin resistance of someone requiring ≥ 200 units/day of insulin. Corrective insulin can still be incorporated into a U-500 regimen based on the blood glucose, but in general, a standard amount of U-500 insulin should be administered two, three, or four times daily, and adjustments are typically made only after the collection of 1 or 2 weeks of blood glucose data. Table 1 indicates

the typical adjustment amounts for each dosing range.

Patients' blood glucose levels often vary significantly through the day, as their caloric and carbohydrate intake varies at different mealtimes. We stress the need for consistency in caloric and carbohydrate content of meals and often give patients target ranges of carbohydrates based on nutritional recommendations. Table 3 provides a sample U-500 regimen that can be adjusted to correct premeal hyperglycemia. Please note, for ease of patient use, the standard meal bolus is incorporated into the patient's correction insulin regimen.

Successful Delivery of U-500 Insulin: Inpatient and Outpatient

Inpatient setting

It is important to remember that, unlike all other forms of insulin, U-500 insulin doses do not correspond to the measurement units on a regular U-100 insulin syringe. U-500 insulin needs to be administered like other volume-injectable medications and should be drawn up and administered via a volumetric syringe. Because of its availability in 0.5-cc and 1-ml sizes, a TB syringe is an appropriate choice, but a 3-cc syringe with attached injection needle can be used for higher volume doses. Thus, doses should be written as a volume per subcutaneous injection, and following the 2007 Institute for Safe Medication Practices Guidelines, the word "CONCENTRATED" should be added to the prescription. For example, if a health care provider intends to prescribe 150 units of insulin three times daily and wants to use U-500 regular insulin, the proper prescription would be "Insulin Human Regular (CONCENTRATED) U-500, 150 units, inject 0.3 ml subcutaneously, three times daily before meals."

The inclination is to use insulin syringes, because U-500 is a type of insulin, and insulin syringes are more readily available. However, the use of insulin syringes, particularly in the hospital setting, can lead to errors and confusion, since the units on insulin syringes do not correspond to the actual units of U-500 insulin being administered. It is imperative

Table 3. Sample U-500 Insulin Regimen*		
Before breakfast (between 7:00 and 10:00 a.m.) and lunch (between 11:00 a.m. and 1:00 p.m.):		
Blood Glucose (mg/dl)	Amount of U-500 Insulin (ml)	Actual Units of Insulin (units)
80–124	0.15 (looks like 15 units on the syringe)	75
125–249	0.2 (looks like 20 units on the syringe)	100
250–299	0.3 (looks like 30 units on the syringe)	150
300–349	0.5 (looks like 50 units on the syringe)	250
350–449	0.6 (looks like 60 units on the syringe)	300
> 449	0.8 (looks like 80 units on the syringe) Call doctor for > 449 mg/dl	400
Before dinner (between 5:00 and 8:00 p.m.):		
80–124	0.08 (looks like 8 units on the syringe)	40
125–199	0.12 (looks like 12 units on the syringe)	60
200–299	0.2 (looks like 20 units on the syringe)	100
300–349	0.3 (looks like 30 units on the syringe)	150
350–449	0.4 (looks like 40 units on the syringe)	200
> 449	0.5 (looks like 50 units on the syringe) Call doctor for > 449 mg/dl	250

*This regimen was designed for a 50-year-old, 100-kg patient with type 2 diabetes. This regimen does not take the place of the basal regimens presented in Table 1 but demonstrates a variation from those templates.

in the hospital setting to administer U-500 insulin in either 0.5-ml or 1.0-ml TB syringes that only have volume markings, or 3-ml syringes with volume markings for doses > 500 units (> 1 ml).

A final suggestion to hospital-based health care providers caring for patients using U-500 insulin: as a validation of the dose, have patients demonstrate when possible or verbally describe on the syringe they use (likely an insulin syringe) how much U-500 they draw up during dosing times. In this validation step, remember that 0.01 ml equals 1

unit of insulin on the insulin syringe. Write the prescriptions correctly, and let patients know how their prescriptions are being written. They need to know that the amount has not changed, just the way it is written so that they will receive the correct dose from all staff.

Outpatient setting

Despite vigilance in using volumetric and TB syringes in the hospital setting, it is worth conceding that U-100 insulin syringes will be used to administer U-500 insulin by patients because of the practical

issues of easy availability of insulin syringes as diabetes supplies and insurance coverage recognizing insulin syringes as a diabetic supply. No matter what syringe patients choose to draw up their U-500 insulin, it is essential to have a specialized health care provider/diabetes educator who is knowledgeable about U-500 insulin show them on the syringe where and how to draw up their dose using the unit markings on the syringe corresponding to their dose. It is also important to use care when writing down the insulin regimen for patients. Patients using insulin syringes need to be able to clearly understand how to measure their doses on an insulin syringe and how to relay their dosing regimen to other health care providers. Providers must stress to patients that they should express the amount of U-500 they inject in terms of volume.

Conclusions

U-500 regular insulin is a useful form of insulin for the management of patients with various forms of diabetes, and this concentrated formulation may also help type 2 diabetic patients with severe insulin resistance achieve their glycemic goals. U-500 insulin alleviates the volume-related problems associated with U-100 insulin, making treatment with higher doses of insulin (> 200 units/day) more effective and more cost-efficient than with U-100 insulin. Following the previously reported and patient-tested algorithm for U-500 delivery and taking care to prescribe and teach patients their doses as volume of insulin to be injected can yield more successful management of hyperglycemia in patients with severe insulin resistance.

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