# The Use of U-500 in Patients With Extreme Insulin Resistance

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The Diabetes Control and Complication Trial (1) and the U.K. Prospective Diabetes Study (2,3), as well as other smaller trials (4), have established the benefit of treating type 1 and type 2 diabetes to levels of glycemia as close to normal as possible. These studies have formed the basis for the therapeutic targets set forth in the most recent American Diabetes Association (ADA) guidelines (5).

There is a subset of patients classified by the ADA as having "other specific types of diabetes"; this group represents a major therapeutic challenge in terms of achieving glycemic goals (6). These patients have more extreme forms of insulin resistance than typical type 2 diabetic patients, and many manifest various syndromic classifications (Fig. 1). Furthermore, for the purpose of this discussion, we are including patients with extreme endogenous hyperinsulinemia or hyperglycemic patients who require doses of exogenous insulin of >200 units/day or in pediatric patients doses >3 units · $kg^{-1}$ · $day^{-1}$. This includes a subset of obese type 2 diabetic patients. Extreme forms of insulin resistance may also occur as a temporary state with pregnancy, with endocrinopathies and under various other stress conditions such as an infection, or with exogenous steroid use (Fig. 2). The practical issue of insulin management is essentially the same for all of these various patient categories.

## Role of insulin therapy for insulin resistance

While we have defined the more extreme forms of insulin resistance whose requirements are >200 units insulin/day, this is clearly an arbitrary definition. Currently glycemic goals for both type 2 diabetes and "the other specific types of diabetes" are generally not being met. Part of the reason for this is that patients clearly are on insufficient doses of insulin. For instance, the median dose of insulin in a group of Pima Indians under treatment is 70 units/day or ~0.7 units · $kg^{-1}$ · $day^{-1}$. At this dose, the median $HbA_{1c}$ is ~9.4% (C. Bogardus, personal communication). This scenario can be broadened to the larger population of diabetic patients. There seems to be a reluctance to use higher doses of insulin for a variety of reasons (7,8). This reluctance is based in part on the knowledge that after 200 units insulin/day, the dose response to further insulin administration is attenuated (Fig. 3). However, this reduced response range does not mean that extremely high doses of insulin are without further effect. Potential adverse effects of insulin therapy include risk of hypoglycemia and weight gain. At the present time, there is no way to completely avoid either hypoglycemia or weight gain with insulin therapy (9). These issues, while important, should not preclude the use of high-dose insulin therapy. One key limitation to the use of high-dose insulin therapy may be simply that the volume of insulin necessary to achieve these very high doses is difficult to administer subcutaneously with U-100 insulin.

Before discussing higher doses of insulin, it is important to reiterate that diet and exercise, as well as oral agents that increase insulin sensitivity, may have value as adjunctive forms of treatment to insulin (10–14). These therapies seem to have their greatest role when the hyperglycemia is associated with obesity, as is the case with almost all type 2 diabetic patients. Diet and oral agents have a more limited value in many of the syndromic forms of extreme insulin resistance, in which obesity is usually not an issue. Oral insulin sensitizer agents may be of value when combined with insulin therapy. In fact, in most circumstances, oral agents are used first and insulin therapy added incrementally in an attempt to reach therapeutic targets (13).

It may be possible to achieve glycemic goals in the majority of type 2 diabetic patients with insulin doses of 0.5–1 unit · $kg^{-1}$ · $day^{-1}$. When the requirement exceeds this amount, the volume may become an important issue, and when doses exceed 3 units · $kg^{-1}$ · $day^{-1}$, the volume of insulin is technically difficult to administer. The volume issue is in part resolved by the use of a more concentrated insulin preparation. Our experience has been with U-500 insulin, which is manufactured by Eli Lilly, but a similar preparation of U-400 insulin is manufactured by Novo Nordisk.

## U-500 insulin therapy in extreme insulin resistance

Our experience has largely been in the treatment of syndromic forms of insulin resistance, but we believe the same principles apply to a larger subset of patients in the "other specific types of diabetes" category. We have treated 43 patients with U-500 insulin (15–21). These patients have syndromic forms of insulin resistance such as type A and type B insulin resistance syndrome, congenital and acquired generalized lipodystrophy, HAIR-AN (hyperandrogenism–insulin resistance–acanthosis nigricans), and Rabson-Mendenhall syndrome (Fig. 4). Eight of these patients are of pediatric age. The doses of insulin have ranged from 1.6 units · $kg^{-1}$ · $day^{-1}$ to >566 units · $kg^{-1}$ · $day^{-1}$. In treating these patients, we have created the algorithm shown in Fig. 5.

While therapeutic targets may not be achievable in these patients, large doses of

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Received for publication 24 January 2005 and accepted in revised form 8 February 2005.
**Abbreviations:** ADA, American Diabetes Association; SMBG, self-monitoring of blood glucose.

| SYNDROME | ACANTHOSIS NIGRICANS | ANDROGEN LEVELS | PCO* | INSULIN LEVELS | TRIGLYCERIDES LEVELS | ETIOLOGY |
|---|---|---|---|---|---|---|
| RABSON MENDENHALL | Yes | ↑↑ | Yes | ↑↑↑ | ↓→ | Mutation of insulin receptor |
| TYPE A | Yes | ↑↑↑ | Yes | ↑↑↑ | ↓→ | Mutation of insulin receptor |
| TYPE B | Yes | ↑↑→ | Yes | ↑↑ | ↓→ | Anti insulin receptor antibody |
| LIPODYSTROPHY | Yes | ↑↑ | Yes | ↑↑ | ↑↑↑ | Genetic mutation and/or acquired form |

**Figure 1—***Syndromic forms of insulin resistance. *PCO, polycystic ovary.*

insulin ameliorate extreme hyperglycemia, its attendant catabolic state, and weight loss. Therapy should also ameliorate the microvascular complications of hyperglycemia by 37% and result in a 21% decrease in the risk of any end point/death related to diabetes with a decrease in $HbA_{1c}$ of 1% (2,3). To achieve therapeutic goals for these patients, novel forms of therapy in addition to insulin are being introduced such as recombinant methionyl human leptin (19).

## Special considerations in the use of U-500 insulin

U-500 is only available as a regular form of insulin. The absorption of human insulin after subcutaneous administration is the rate-limiting step of insulin activity. Most of the variability of insulin absorption is correlated with blood flow differences depending on the site of injection. Insulin U-500 appears to have less day-to-day variation in absorption rates and also less absorption variation from the different body regions (see also drug insert details from Humulin R U-500, PA 3050 AMP; Eli Lilly, 2000) (22).

The onset, peak, and duration of effect are the most clinically significant differences among the available forms of insulin. Regular U-100 insulin has a peak effect 2–4 h after administration and duration of action of 5–7 h. U-500 has a pharmacokinetic profile more closely simulating NPH than regular U-100. U-500 insulin does not have anything added during its preparation to change its onset of action from regular U-100 insulin, but it has a more prolonged duration of action of up to 24 h compared with other regular insulins (3). In patients with insulin receptor abnormalities, the duration is even more prolonged because of a deficiency of insulin degradation.

The pharmacodynamics of regular, NPH, and lente insulins are particularly affected by the volume of the dose (3,22). Larger doses can cause a delay in the peak and increase the duration of action. For example, injecting 4 units NPH will have a significantly different time-action profile compared with 30 units NPH.

The clinical use of U-500 insulin requires injections be given at least twice daily, i.e., prebreakfast and predinner. The objective goal of therapy is to approach ADA targets for $HbA_{1c}$. With respect to self-monitoring of blood glucose (SMBG), hypoglycemia is not a major problem in patients with extreme insulin resistance. However, if it occurs, it will most likely be in the morning after an overnight fast. The morning SMBG goal for blood glucose is 70–120 mg/dl. If the values are <70 mg/dl, the predinner dose (or last dose of the day) should be adjusted downward. If values are high, then all doses should be adjusted upward. The SMBG should not be used to determine each dose of injected insulin but should be used over several days to determine a pattern. SMBG taken prebreakfast and predinner is usually sufficient. Intensive SMBG and carbohydrate counting do not determine the individual dose, which is the more conventional practice. When the total daily dose of insulin is ≥300 units/day, this is best delivered by giving U-500 three times a day. When the total daily dose is >750 units/day, the prescriber should look to adding a bedtime dose of U-500. The amount of the bedtime dose should be less than the three

1. Type 1 Diabetes
2. Type 2 Diabetes
3. Other specific types
   - a)Genetic defects of β cell function
   - **b) Genetic defects in insulin action**
   - c)Disease of the endocrine pancreas
   - **d)Endocrinopathies**
   - e)Drug or chemical induced
   - f)Infections
   - **g)Uncommon forms of immune-mediated diabetes**
   - **h)Other genetic syndromes associated with diabetes**
4. Gestational Diabetes Mellitus (GDM)

**Figure 2—***Etiologic classification of diabetes. Categories in bold are related to U-500 insulin therapy.*

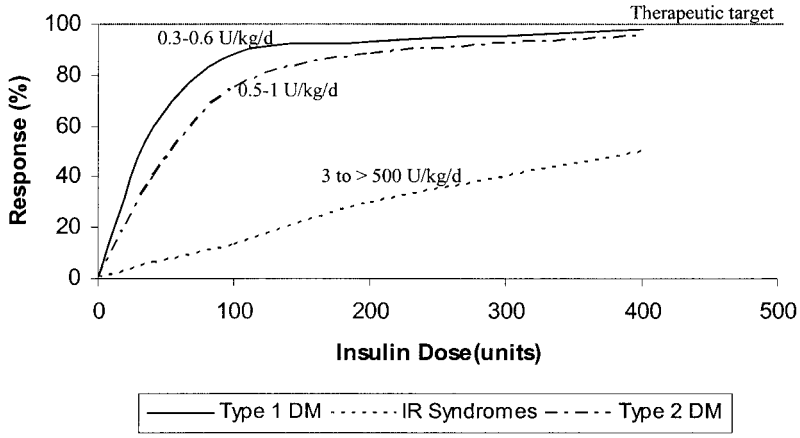


**Figure 3**—*Theoretical total body insulin dose-response curve for insulin administration. Each curve is the composite of total body glucose uptake and hepatic output suppression. Representative dose ranges of daily insulin administration to achieve target goals are shown, i.e., 0.3–0.6 units · $kg^{-1}$ · $day^{-1}$ for type 1 diabetes (DM), 0.5–1 unit · $kg^{-1}$ · $day^{-1}$ for type 2 diabetes, and 3 to >500 units · $kg^{-1}$ · $day^{-1}$ for syndromic insulin resistance (IR). Note that in type 2 diabetes and insulin resistance syndromes, the dose response at the target levels are marked attenuated. Thus, much higher doses of insulin are required to achieve or approach target goals. The values of type 1 and type 2 diabetes are derived from the literature, and the values for the syndromic forms are taken from our own experience.*

previous doses, in order to minimize morning hypoglycemia. Total daily doses of ≥2,000 units may warrant usage of an insulin pump (23–25) (Fig. 5).

Extreme insulin-resistant states are sometimes temporary, and the need to taper the U-500 and switch back to U-100 insulin may be warranted. The algorithm can be followed in the reverse, except in the final steps. We have had the most sustained success in switching patients back to U-100 regular insulin from U-500 insulin when the total daily dose is ≤175 units. This again appears to be volume related.

An important caveat that must be taken into consideration is the syringe for administration of U-500. Unlike U-100 insulin, the dose of U-500 does not equal the units of insulin using a typical insulin syringe. For example, if a patient requires 150 units insulin three times a day, and the prescriber wishes to use U-500, the correct way to write the prescription is as follows: "Regular Insulin U-500, 150 units, inject 0.3 ml subcutaneously, three times daily before meals." Using this example, confusion will arise, because a patient will be told to "draw up 30 units of insulin," and patients inevitably believe that their dose of insulin is 30 units, rather than 0.3 ml U-500 or 150 units. To help avoid this confusion, a tuberculin syringe can be used, which has volume markings instead of unit markings. This, however, may only be practical in the hospital-based setting. Tuberculin syringes are not as readily available for the patient to purchase at his/her local pharmacy. Insurance reimbursement of an insulin syringe versus a tuberculin syringe is more established, as insulin syringes are seen as part of diabetic supplies. It is critical, therefore, when using a U-100 syringe to explain the amount to be taken in both dose and volume terms.

## Cost analysis and availability of U-500 insulin

Knee et al. (23) report a cost savings of U-500 insulin versus insulin lispro (Fig. 6). Despite U-500 costing more per milliliter, there is a reduction in the volume of insulin used with U-500, which translates into a reduced cost per unit of insulin versus other forms of insulin. This also does not take into account the additional cost savings of needing fewer syringes to inject the smaller volumes of insulin and/or fewer pump cartridge changes if using a concentrated form of insulin in an insulin pump. Furthermore, U-500 insulin is used alone, which represents an additional price savings because patients are usually on other repository forms of insulin when using U-100 regular and U-100 insulin lispro. U-500 insulin is unlikely to be immediately available in most regular pharmacies, as would be expected for the more conventional insulin preparation. However, by appropriate prearrangement with the pharmacy, it can usually be obtained in 24–48 h.

## Summary

Using the technology available today and available insulin preparations, it would

**NIH PATIENTS TREATED WITH U-500 INSULIN**

| SYNDROME | PATIENTS | DOSE RANGE | WEIGHT * | REFERENCE |
|---|---|---|---|---|
| | Number | U/Kg/d | Kg | |
| TYPE A | 5 | 6 - 566 | 58.2 | 18, 21 |
| Rabson-Mendenhall | 3 | 18 - 80 | 28.3 | 17, 18 |
| TYPE B | 24 | 3.3 - 416 | 78.6 | 16 |
| Generalized Lipodystrophy | 9 | 3.3 - 21 | 61.5 | 15,19,20 |
| HAIR-AN** | 2 | 1.6 - 4.1 | 125.1 | UNPUBLISHED |

**Figure 4**—*National Institutes of Health patients treated with U-500 insulin. *Mean weight of each group. **HAIR-AN, hyperandrogenism–insulin resistance–acanthosis nigricans.*

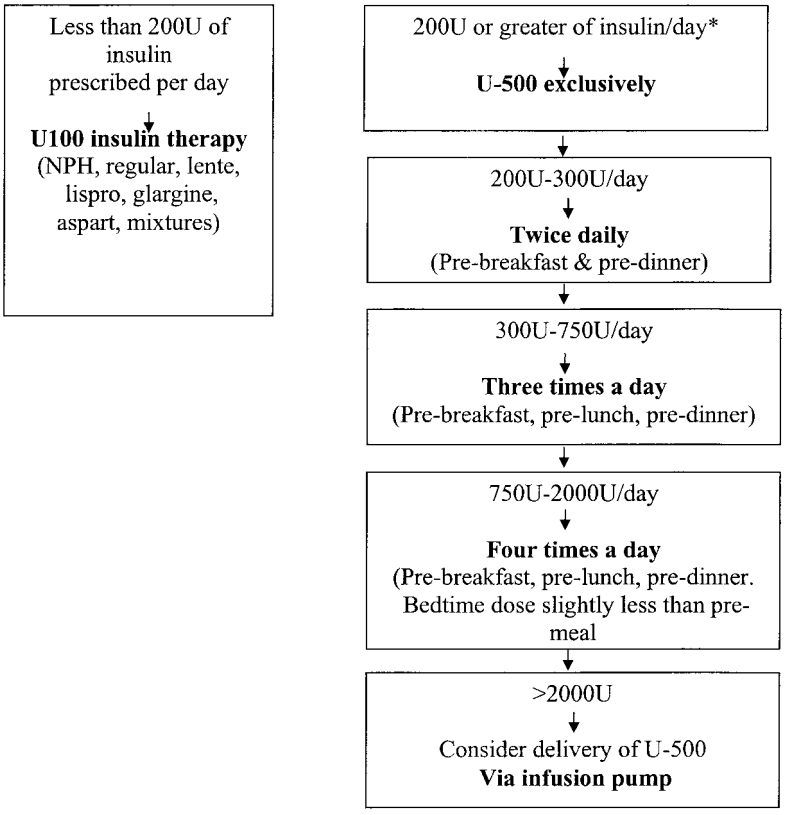


**Figure 5—***Algorithm for insulin therapy based on units of insulin administered per dose. Each of these approaches could be combined with oral agent (i.e., metformin or thiazolidinediones). *Pediatric patients doses >3 units · kg$^{-1}$ · day$^{-1}$.*

appear that progress has been made in treating type 1 diabetes and that therapeutic targets are being approached with dose ranges of insulin from 0.3 to 0.6 units · kg$^{-1}$ · day$^{-1}$. In "other specific types of diabetes" and in a subset of type 2 diabetes, this does not appear to be the case. It is clear that at least 40% of all diabetic patients will require insulin therapy to achieve therapeutic targets (7,8,26,27). In that the targets are not being met, it must mean an insufficient number of patients are treated with insulin and/or the doses of insulin are not sufficient.

In patients who take insulin, one limitation may be the volume of insulin necessary to achieve a dose capable of reaching the therapeutic target. We have presented an algorithm from our experience in treating syndromic forms of insulin resistance. We believe the algorithm is relevant in an increasing number of patients with type 2 diabetes, who also demonstrate severe insulin resistance. The use of U-500 insulin may be another treatment option in helping severely insulin-resistant, type 2 diabetic patients reach their desired therapeutic targets.

| Insulin | Unit of issue | Price per vial (in U.S. dollars) | Price per mL (in U.S. dollars) | Price per unit (in U.S. dollars) |
|---|---|---|---|---|
| U-100 Insulin Regular | 10 mL vial | $30.74 | $3.07 | $0.31 |
| U-100 Insulin Lispro | 10 mL vial | $67.16 | $6.71 | $0.67 |
| U-500 Insulin Regular | 20 mL vial | $210.68 | $10.53 | $0.21 |

**Figure 6—***Cost analysis of insulin preparations.*

**Acknowledgments**— We thank Drs. Clifton Bogardus and Judith Fradkin for their helpful comments in the preparation of the manuscript. We also thank the Clinical Center Pharmacy Department for help in the formulation of the cost analysis.

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