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

ELAINE COCHRAN, MSN, CRNP
CARLA MUSSO, MD
PHILLIP GORDEN, MD

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 doses of insulin have ranged from 1.6 units · kg⁻¹ · day⁻¹ to >566 units · 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

From the Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

Address correspondence and reprint requests to Elaine Cochran, CRNP, CEB/NIDDK/NIH, 9000 Rockville Pike, Bldg. 10, CRC 6-5940, Bethesda, MD 20892. E-mail: elainec@ntra.niddk.nih.gov.

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.

© 2005 by the American Diabetes Association.
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 \( \text{HbA}_1c \) 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 \( \text{HbA}_1c \). 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 \( \geq 300 \) 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

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>ACANTHOSIS NIGRICANS</th>
<th>ANDROGEN LEVELS</th>
<th>PCO*</th>
<th>INSULIN LEVELS</th>
<th>TRIGLYCERIDES LEVELS</th>
<th>ETIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>RABSON MENDENHALL</td>
<td>Yes</td>
<td>↑↑</td>
<td>Yes</td>
<td>↑↑↑</td>
<td>↓→</td>
<td>Mutation of insulin receptor</td>
</tr>
<tr>
<td>TYPE A</td>
<td>Yes</td>
<td>↑↑↑</td>
<td>Yes</td>
<td>↑↑↑</td>
<td>↓→</td>
<td>Mutation of insulin receptor</td>
</tr>
<tr>
<td>TYPE B</td>
<td>Yes</td>
<td>↑↑→</td>
<td>Yes</td>
<td>↑</td>
<td>↓→</td>
<td>Anti insulin receptor antibody</td>
</tr>
<tr>
<td>LIPODYSTROPHY</td>
<td>Yes</td>
<td>↑↑</td>
<td>Yes</td>
<td>↑</td>
<td>↑↑↑</td>
<td>Genetic mutation and/or acquired form</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>PATIENTS</th>
<th>DOSE RANGE</th>
<th>WEIGHT *</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE A</td>
<td>5</td>
<td>6 - 566</td>
<td>58.2</td>
<td>18, 21</td>
</tr>
<tr>
<td>Rabson-Mendenhall</td>
<td>3</td>
<td>18 - 80</td>
<td>28.3</td>
<td>17, 18</td>
</tr>
<tr>
<td>TYPE B</td>
<td>24</td>
<td>3.3 - 416</td>
<td>78.6</td>
<td>16</td>
</tr>
<tr>
<td>Generalized Lipodystrophy</td>
<td>9</td>
<td>3.3 - 21</td>
<td>61.5</td>
<td>15, 19, 20</td>
</tr>
<tr>
<td>HAIR-AN**</td>
<td>2</td>
<td>1.6 - 4.1</td>
<td>125.1</td>
<td>UNPUBLISHED</td>
</tr>
</tbody>
</table>

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

**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.

**References**


12. Knowler WC, Barrett-Connor E, Fowler...
1244


