Delayed Response to U-500 Regular Insulin

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Severe insulin resistance was defined 45 years ago as a daily insulin requirement of >200 units (1) and, more recently, as an insulin requirement >2 units/kg/day (2). Because severely insulin-resistant patients require large amounts of insulin, the corresponding injection volume of traditional U-100 insulin is also large. In addition to the inconvenience to patients of having to take an increased number of injections, insulin absorption from large injectate volumes is impaired (3–5). For these reasons, increasing numbers of severely insulin-resistant patients, whose insulin resistance is most often due to obesity, are being treated with U-500 regular insulin (6).

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of U-500 regular insulin more closely resemble those of NPH insulin than of U-100 regular insulin (2,7). Therefore, we adjust the doses of U-500 regular insulin using the same principles as are used for NPH insulin given before breakfast and supper, only with greater dose changes. Our algorithm for using U-500 regular insulin is shown in Figure 1. Not shown in the figure is the situation in which the prebreakfast and presupper glucose levels meet target values but A1C levels are still above target. In that case, patients are asked to measure their blood glucose levels before lunch and before their bedtime snack, and short- or rapid-acting insulin is added in separate injections if those glucose values are high.

Those of our patients who have fairly consistent eating patterns and whose glucose is not controlled with noninsulin medications plus U-100 basal or bedtime NPH insulin are given a choice of a less flexible, two-injection self-mixed/split intensified insulin regimen or a more flexible basal/bolus regimen of up to four daily injections. Many select the two-dose regimen. Occasionally, a patient has a delayed response to the NPH insulin (8,9). This becomes apparent when low fasting self-monitoring of blood glucose (SMBG) values remain low or at target despite markedly decreasing the evening NPH insulin dose. Eventually, overnight glycemia is managed satisfactorily by the prebreakfast NPH insulin dose without any evening dose. Because of the delayed peak of NPH insulin, a large proportion of the effect of the morning injection occurs overnight; therefore, these patients often require prelunch short- or rapid-acting insulin to control afternoon glycemia. Because they also require prebreakfast and presupper short- or rapid-acting insulin to control morning and evening glycemia, respectively, their insulin regimen essentially becomes a basal/bolus one with the prebreakfast NPH insulin acting as the basal insulin (8,9).

The case presented below is our first experience with a delayed response to U-500 regular insulin.

Case Presentation

At the time this female patient with a BMI of 33.3 kg/m^2 was switched to

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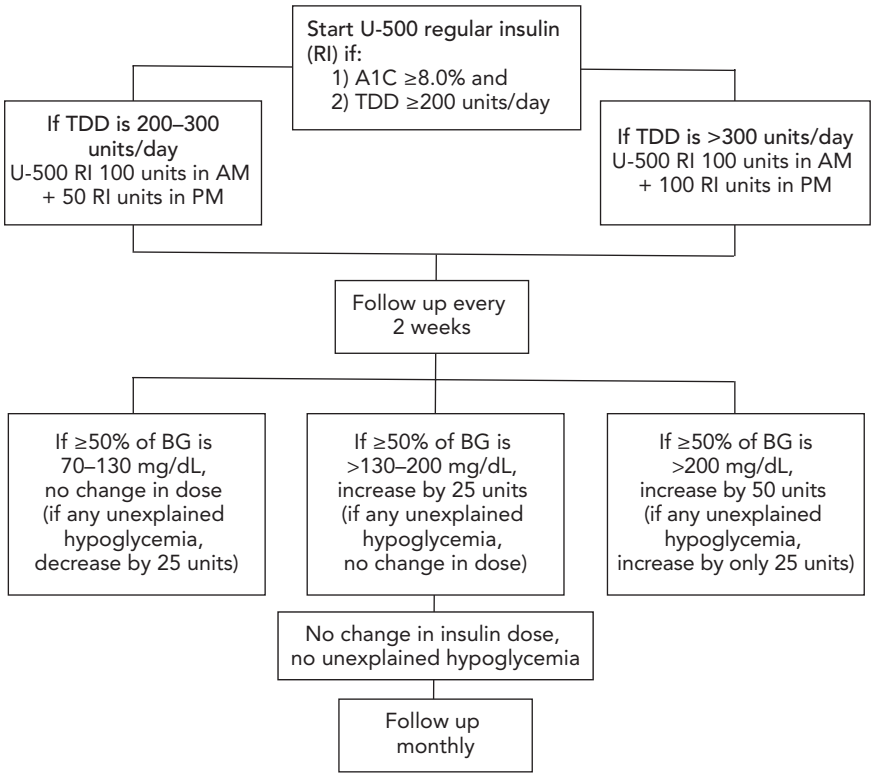

FIGURE 1. Algorithm for starting and adjusting U-500 regular insulin doses. Unexplained hypoglycemia includes episodes that are not explained by delayed, smaller than usual, or missed meals; increased exercise; or having taken an incorrect insulin dose. BG, blood glucose; TDD, total daily dose. Reprinted with permission from *Diabetes Care* 2007;30:455.

U-500 regular insulin in June 2011, she was taking 218 units of insulin in a self-mixed/split regimen, her total daily dose was 2.8 units/kg, and she had had diabetes for 11 years. Her A1C just before being placed on U-500 insulin was 9.4%. According to the algorithm (Figure 1), she was started on 100 units before breakfast and 50 units before supper. Her doses of U-500 regular insulin quickly increased to 200–250 units in the morning and 75 units in the evening. Her morning dose remained in that range until December 2013, when it increased to 275 units and remained so until November 2014, when it was increased to 325 units. In September 2015, she switched herself to glargine insulin, but 2 weeks later returned asking to be placed back on U-500 insulin because her glucose levels had become quite high. She was placed on 200 units before breakfast (with no evening dose) and has remained on that amount.

Her presupper dose of U-500 insulin remained at 75 units until August 2012, when it began to be gradually decreased until it was discontinued in December 2013. Her fasting plasma glucose (FPG) values per SMBG before breakfast after the various evening doses of U-500 insulin are shown in Table 1. The median values are similar regardless of the size of the evening doses or even without any U-500 regular insulin in the evening.

As with patients with a delayed response to U-100 NPH insulin, this patient also required a rapid-acting insulin (lispro) before each meal. The doses started out low but were increased to 30–40 units before each meal. Between September 2011 and February 2016, her A1C was measured 28 times with a range of 7.3–8.5% and a median of 8.2%.

Questions

1. Since the PK/PD characteristics of U-500 regular insulin closely resemble those of U-100 NPH insulin, why were prebreakfast SMBG values within target as presupper U-500 regular insulin was progressively decreased and eventually discontinued?
2. Likewise, why was U-100 rapid-acting insulin necessary before lunch to control the presupper SMBG values when the patient was receiving such high doses of U-500 regular insulin (200–375 units) before breakfast?
3. Is it possible that an occasional patient has a delayed response to U-500 regular insulin, as occasionally happens in patients taking U-100 NPH insulin?

Commentary

The conditions associated with severe insulin resistance are listed in Table 2 (10). This patient had no evidence of an ongoing infection lasting for years nor of ingestion of a drug antagonizing the effect of insulin that could account for her insulin requirements, which fulfilled the definition of severe insulin resistance. She did not have acanthosis nigricans, and her immunoglobulin G (IgG) insulin antibody was negative. Her response to the U-500 regular and lispro insu-

TABLE 1. Self-Monitored FPG Concentrations After Different Evening U-500 Insulin Doses

Evening dose (units)	75	50	25	10	0
Values (*n*)	140	150	49	14	225
Median FPG (mg/dL)	92.0	79.0	98.0	97.5	94.0

TABLE 2. Conditions Associated With Severe Insulin Resistance (10)

- Acanthosis nigricans
- Acromegaly
- Cushing's syndrome
- Hemochromatosis
- Immune-mediated (by IgG antibody)
- Infections
- Insulin degradation at injection site
- Lipodystrophic diabetes
- Obesity
- Werner's syndrome (adult form of progeria)

lins rules out insulin degradation at the injection site. Furthermore, there was no clinical evidence of the other conditions in Table 2, except for her obesity.

To my knowledge, this is the first reported case of a delayed peak of action of U-500 regular insulin. It followed the same pattern that has been seen in a delayed response to U-100 NPH insulin (i.e., continued low or at-target SMBG values before breakfast as the evening dose was decreased and finally discontinued, along with the requirement of preprandial bolus doses before each meal) (8,9).

Because a number of our patients with a delayed response to U-100 NPH insulin responded appropriately to relatively low doses of lispro insulin (<30 units), I had postulated that the delayed peak of action of the U-100 NPH insulin probably involved the interaction between the insulin and protamine in the preparation (8,9). (The slowed release of insulin from protamine is responsible for the PK/PD of NPH insulin.) Given this mindset, the nurse practitioner who followed this patient and I failed to consider a delayed response to U-500 regular insulin for more than a year.

Clearly, the postulate concerning a markedly delayed release of insulin from the protamine in the NPH insulin preparation is not tenable here, and the cause of the delayed response to U-500 regular insulin in this patient is unclear. In any event, providers who use this insulin preparation should be alerted to the unusually delayed peak of action of U-500 regular insulin noted in this patient and tailor their treatment approach accordingly for similar patients.

Clinical Pearls

- A delayed response to U-500 regular insulin can occur in an occasional patient, as it can in those taking U-100 NPH insulin.
- It is identified in a similar manner, with SMBG values before breakfast remaining in the target range as presupper U-500 regular insulin is progressively decreased and eventually discontinued.
- Because the major effect of U-500 regular insulin in this situation occurs overnight, increasing doses before breakfast does not control the presupper SMBG values (and may cause overnight hypoglycemia), necessitating preprandial short- or rapid-acting U-100 insulin.
- The insulin regimen in patients with a delayed response to U-500 regular insulin essentially is a basal-bolus one, with the U-500 regular insulin functioning as the basal insulin.

Duality of Interest

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

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