Commentary

THE USE OF HIGHLY CONCENTRATED U-500 REGULAR INSULIN FOR THE SEVERELY INSULIN RESISTANT PATIENT WITH TYPE 2 DIABETES

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Abbreviations:
HbA1c = glycated hemoglobin; **U-500R** = 500IU/mL regular insulin

Severe insulin resistance is defined as requiring >200 IU of insulin or more than 2 IU/kg body weight per day. With the increasing burdens of diabetes and obesity, the number of patients fulfilling these criteria has progressively increased. The treatment of these patients is difficult, and the use of standard U-100 insulin preparations requires the injection of very large volumes of insulin multiple times a day. Not surprisingly, glycemic control is difficult to attain in this patient group.

Regular human insulin 500 IU/mL (U-500R) has been available as a therapeutic option since 1995. Due to the relative infrequency of severe insulin resistance, most reports of the use of U-500R consist of retrospective surveys of small numbers of patients; very few prospective studies of the efficacy of this insulin preparation have been published. Nevertheless, all available literature points to improvements in glycemic control, with glycated hemoglobin (HbA1c) reductions between 1 and 3.5%. Additionally, reports suggest better quality of life and patient preference, as well as greater medication adherence when U-500R is used appropriately in properly selected patients. While still relatively infrequently used, prescriptions for U-500R almost doubled in the U.S. between August 2008 and September 2010.

Although U-500R is, in essence, nothing more than a highly concentrated form of regular insulin, the increased concentration significantly alters its pharmacokinetics, with the attenuated duration of action of U-500R approaching that of neutral protamine Hagedorn insulin. Thus, the use of U-500R requires a "mind-shift" in the approach of the prescribing physician. The tendency to use U-500R as an alternative "bolus" insulin before meals should be avoided, as should the use of U-500R together with "basal" U-100 insulin. Rather, U-500R should be used as an intermediate-acting insulin. Most patients will improve glycemic control using this insulin twice daily, but dosing will depend on the total daily insulin requirements of the patient (see Fig. 1)(1). A few reports describe the use of U-500 in insulin pumps as continuous subcutaneous insulin infusion therapy, which is the recommended delivery mode in those rare patients requiring in excess of 2,000 IU of insulin daily. While the reported results are encouraging, the duration of action and action profile of U-500R is such that only a basal rate is required in many cases. With this in mind, the use of the V-Go® insulin pump, as used in the case report by Kennedy and Tannock published in this issue (1), offers a simple and potentially useful alternative for these patients.

When converting a patient from U-100 insulin to U-500R, the general recommendation is to reduce the total insulin dose by 10% if the HbA1c is below 7.5%. If the HbA1c is between 7.5 and 8.5%, the total daily insulin dose may remain unchanged, and the dose should be increased by 10% if the HbA1c is above 8.5%. The number of daily injections required will depend upon the total daily dose requirements (2). The total daily dose should initially be split equally between the number of daily injections and thereafter titrated according to the Home Glucose Monitoring profile. Some benefit may be obtained by using insulin sensitizers such as metformin with U-500R, but the advantages of combining U-500R with other oral agents

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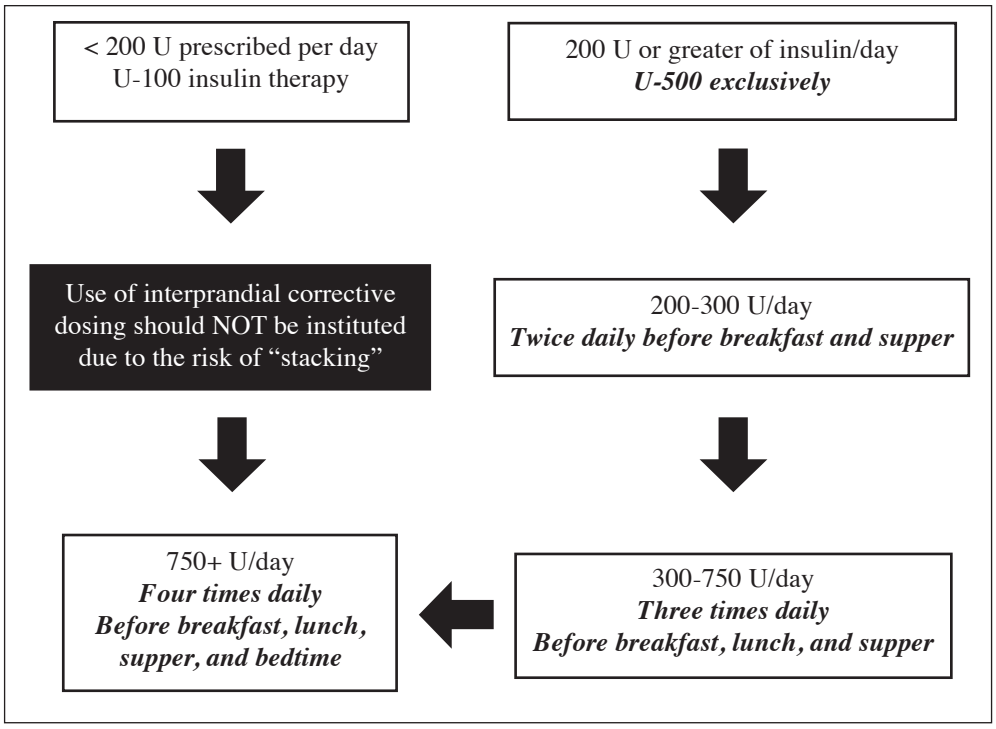

Fig 1. Dosage recommendations for U-500R insulin use. Adapted from (2)

such as dipeptidyl peptidase-4 inhibitors of sulfonylureas is not established. The available literature suggests that liraglutide (but not exenatide) may enhance glycemic outcomes in these patients.

One of the major barriers to the successful use of U-500 insulin is the concept of the insulin being 5 times more potent than the standard U-100 formulation. As no U-500 insulin syringes are available, either tuberculin syringes or U-100 insulin syringes must be used. This creates the problem of patients (and practitioners) understanding that a 1-IU increment on the delivery-device dose scale will actually result in the administration of 5 IU of insulin. For accuracy, we often recommend the use of a 0.5- or 0.3-mL insulin syringe depending on the required dose. Most importantly, extensive and intensive patient education and training is needed with this highly concentrated form of insulin. Using a combination of U-500R and U-100 insulin may further compound these difficulties and result in errors. In any event, once a patient requires over 200 IU of insulin daily and takes U-500R, there is little reason to combine it with U-100 insulin. Although the combination of U-500R and U-100 insulin has been reported, most case series report the use of U-500R by itself, with or without an insulin sensitizer such as metformin.

Both weight gain and increased rates of hypoglycemia might be anticipated with the improvement in glycemic control achieved using U-500 insulin. Indeed, a degree of weight gain was noted in mose of the reported series. Although this is usually modest (not more than 5 kg), significant excessive weight gain may occur in some individuals. Most series report an increased frequency of hypoglycemia as glycemic control improves. Importantly, however, no increase in major hypoglycemic events has been reported with the use of U-500R.

DISCLOSURE

The author has no multiplicity of interest to disclose.

REFERENCES

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