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Role of Human Regular Insulin U-500 in Treatment of Patients with Type 2 Diabetes

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Abstract

Background: Human regular insulin 500 (U-500) is a form of concentrated insulin that allows injection of high insulin doses with 5 times less volume compared with traditional regular insulin (U-100).

Methods: Review of all pertinent clinical studies related to insulin U-500.

Results: Insulin U-500 is indicated in patients with type 2 diabetes who require more than 200 units of insulin per day. This concentrated insulin has both prandial and basal actions, and can be injected as monotherapy in a convenient twice-daily regimen. Available data suggest that insulin U-500 is effective, associated with better compliance, and decreased injection pain compared with non-concentrated insulins. Its main limitations are hypoglycemia and weight gain, and possibility of dosing errors.

Conclusions: Overall, insulin U-500 is an effective and safe treatment for patients with type 2 diabetes and insulin resistance. Randomized trials are needed to compare long-term efficacy and safety of insulin U-500 with other forms of insulin regimens.

Keywords: Concentrated Insulin; Efficacy; Insulin U-500; Pharmacodynamics; Pharmacokinetics; Safety

Introduction

Many patients with insulin-resistant type 2 diabetes, particularly morbidly obese, require large doses of insulin for glycemic control. Meanwhile, most insulin preparations are present in concentrations of 100 units/ml. Therefore, a patient who needs one insulin dose of more than 100 units has to use more than one injection. Insulin U-500 is a human regular insulin preparation that is 5 times more concentrated than the commonly used human regular insulin (U-100). Therefore, insulin U-500 contains 500 units of insulin per ml as opposed to 100 units/ml in non-concentrated insulins. This concentrated formulation allows the injection of large insulin doses of greater than 100 units be delivered in the fifth amount of volume of non-concentrated insulin. Insulin U-500 (Humilin R U-500) was approved by the Federal Drug Administration (FDA) in the USA in 1994 for insulin-resistant patients with type 2 diabetes who require more than 200 units of insulin per day [1]. Because of rise in incidence of obesity in the USA, the use of U-500 has been increased approximately 10 fold from 2005 to 2013 [2]. The purpose of this article is to describe the drug profile of insulin U-500 and its uses in diabetes based on the available data and author's experience.

Pharmacokinetics and Pharmacodynamics

In healthy obese subjects, mean onset and duration of action of insulin U-500 are 15 min and 21 h, respectively, using 2 doses of 50 and 100 units [1]. The median peak plasma insulin levels occurred between 4 hours (50-unit dose) and 8 hours (100-unit dose) [1]. However, in patients with type 2 diabetes, Shresta et al [3] found that onset of action of U-500 takes longer time: 2.2 h and 2.5 h with 200 units and

100 units of insulin U-500, respectively with no significant difference between the 2 doses. Moreover, the duration of action of the 200 unit-dose was significantly longer than the 100-unit dose, 16.5 h and 11.0 h, respectively [3].

Because of the smaller surface area of concentrated insulins, they take longer time to diffuse into subcutaneous tissues and reach capillaries to get absorbed [4]. Thus, concentrated insulins are absorbed slower than non-concentrated insulin [4]. In healthy obese subjects, de La Pena [5] reported that, compared with regular insulin (U-100) at doses of 100 units, time to peak concentration and time to maximum effect were significantly longer with insulin U-500 than U-100 [5]. In addition, maximum plasma concentrations (Cmax) of U-500 were significantly less than U-100, and its duration of action was longer (21.5 hours versus 18.3 hours for U-100) leading to a flat time-action profile [5]. Mean half-life after a single 100-unit dose is approximately 4.4 h for U-500 versus 3.3 h for U-100 [5].

Available Preparations of Insulin U-500

Insulin U-500 is dispensed in a 3 ml pen (1,500 units) or in a 20 ml-vial (10,000 units), with maximum insulin doses delivered in a single injection of 300 and 250 units, respectively [1]. Both pen and vial delivers insulin U-500 in 5-unit increments [1].

Efficacy of Insulin U-500

Available data suggest that U-500 is effective, but the degree of efficacy is variable depending on several factors: insulin doses, patients' characteristics, and baseline values of hemoglobin A1C (HbA1c). A meta-analysis of 9 studies (8 studies were retrospective) including 310 patients reported significant HbA1c reduction ranging 1.0-3.29% after using insulin U-500, with overall HbA1c reduction of 1.59% [6]. Unfortunately, randomized trials designed to compare insulin U-500 with other types of insulin regimen are not yet available. One randomized trial compared U-500 given BID with U500 given TID [7]. After 24 weeks, there was no significant difference in HbA1c reduction, 1.12% and 1.22% in the TID and BID regimen, respectively [7].

Safety of Insulin U-500

Similar to other insulins, the 2 most common adverse effects of U-500 are hypoglycemia and weight gain. Yet, because of lack of head to head comparison between U-500 and other insulins, the specific impact of U-500 on these 2 parameters is not clear. Hood et al [7] found higher frequency of nocturnal hypoglycemia (blood glucose <50 mg/dl) in patients randomized to U-500 given BID compared with TID, 36% and 49%, respectively. Likewise, symptomatic hypoglycemia (blood glucose < 70 mg/dl) occurred slightly more frequently among the BID group (92%) compared with TID group (90%) (P=0.003), but severe hypoglycemia was similar in the 2 groups [7]. In the previous study, weight gain was 4.9 kg and 5.4 kg in the 2 groups of patients randomized to U-500 TID and BID, respectively [7].

Patient Satisfaction

Patients who switched from multiple insulin injections (median 5 injections/day) to insulin U-500 reported improvement in treatment burden, daily life and compliance, particularly with the BID regimen compared with the TID regimen [8]. Moreover, there was significant improvement in injection site pain from baseline to end of trial at week 24 whether U-500 was given BID or TID [8].

Indications and Initiation of Insulin U-500

Candidates for U-500 are insulin-resistant patients with type 2 diabetes requiring more than 200 units of insulin/day. These patients are commonly morbidly obese and already receiving high number (5-7) of insulin injections/day. Before the conversion of prior insulin regimen to U-500, it is crucial to confirm the actual insulin doses taken by patient because incomplete adherence to insulin therapy is not uncommon as result of increase injection burden. It is safer therefore to reduce insulin daily doses by ~ 20% or more when converting to insulin U-500 to avoid hypoglycemia and to account for possible prior non-adherence [9]. It should be emphasized that the time action profile of insulin U-500 exhibits both prandial and basal effects [1]. Therefore, it is not necessary to combine insulin U-500 with short-acting insulins. Although BID dosing was associated with more frequent hypoglycemia compared with TID dosing in one study [7], BID dosing is optimum for efficacy and adherence [7]. In addition, de la Pena et al showed that BID dosing results in fairly stable basal insulin effect throughout the 24 h [10]. Once-daily dosing is not indicated as the duration of action of insulin U-500 does not last 24 h [3]. Thus, a practical approach is to divide the U-500 total daily dose into 2 portions: 60% of the dose 30 min before breakfast and 40% 30 min before dinner to decrease the incidence of nocturnal hypoglycemia.

Use of Insulin U-500 in Hospitals

The use of U-500 is not indicated in hospitalized patients to avoid dosing errors. When a patient taking insulin U-500 is admitted to the hospital, it is safer to switch to a non-concentrated insulin regimen. Because food intake in hospitals is much less compared with home, it is recommended to decrease the initial total daily dose of insulin U-500 by 50% or more after hospital admission [11,12].

Use of Insulin U-500 in Pregnancy

Pregnancy is considered an insulin-resistant state. The largest study that reported use of insulin U-500 in pregnancy was a retrospective including 73 women switching from conventional insulin to insulin U-500 during pregnancy [13].

Following switching, frequency of hypoglycemia was more common with use of U-500. Thus, percentage of recorded blood glucose values < 60 mg/dl increased from 2.0% to 4.8%, and values <50 mg/dl increased from 0.7% to 2.0% after switching [13]. However, insulin doses before versus after initiation of insulin U-500 were not mentioned [13]. Interestingly, pregnancy and neonatal outcomes were similar among the group of patients receiving U-500 and another comparison group of 78 pregnant patients treated with conventional insulin [13].

Delivery of Insulin U-500 via Insulin Pump

The use of insulin U-500 in insulin pump was evaluated in several pilot studies of patients with type 2 diabetes and insulin resistance. In one study, Lane [14] reported a reduction in HbA1c levels of 1.14% in 9 patients 3 months after switching to insulin U-500 delivered via insulin pump. No clinically severe hypoglycemia (defined as blood glucose <50 mg/dl) were reported [14]. In one meta-analysis including 55 patients, the reduction in HbA1c was 1.64% 3-30 months after starting U-500 by continuous subcutaneous infusion delivered by the insulin pump [6]. The use of insulin U-500 in pump reduces the frequency of changing insulin cartridge from twice a day to once every 3 days, and was associated with higher patient satisfaction compared with using U-100 in the pump or using multiple insulin injections [14]. However, the use of U-500 in insulin pumps is not approved by the FDA. In fact, none of the available insulin pumps are calibrated for use with concentrated insulin, leading virtually to dosing errors.

Cost of Insulin U-500

The whole price sale of 20 ml vial (10,000 units) of U-500 and the 3-ml Kwik-pen (1,500 units) is approximately $ 1,200 and $ 303, respectively [15]. Although these prices are higher than regular insulin U-100, using a large healthcare claims database in the USA, Eby et al [16] showed that treatment with insulin U-500 was associated with significant decreases in pharmacy and overall costs, and better adherence compared with treatment with high-dose (>200 units/day) of insulin U-100 [16]. Moreover, there was no significance difference between the 2 insulin regimens in hypoglycemia-specific costs and in resource utilization [16].

Limitations of U-500

Dosing errors may occur if patient is not properly informed about the concept of insulin U-500, and if this insulin is injected by syringes of non-concentrated insulin. Propensity of dosing errors has greatly diminished after the introduction of a dedicated syringe, specifically graduated for U-500 injection. This U-500 specific syringe was approved by the FDA, and is commercially available since 2016. It is a 0.5 ml green-capped syringe with bold markings in 5-unit increments allowing a maximum dose of 250 units at one injection [17]. In addition, in 2016, the FDA approved the U-500 R Kwik-pen [1]. This pen can provide up to 300 units per dose, but is more expensive than the dedicated syringe.

Advantages and limitations of U-500 are summarized in Table 1.

Advantages	Limitations
Lesser number of injections per day, usually 2 injections	No head to head trials comparing U-500 with other insulin regimens.
Works as basal/bolus insulin so can be used as monotherapy	Requires comprehensive patient education to avoid dosing errors
Can be delivered by a dedicated syringe or a pen	High cost, especially with the Kwiq-pen U-500
May be associated with less pain compared with non-concentrated insulin	
High patient satisfaction and adherence	
Can be used during pregnancy	

Table 1: Advantages and limitations of insulin U-500.

Conclusions and Future Needs

Insulin U-500 is the most concentrated available form of insulin allowing the reduction of injected volume of insulin by one-fifth. This insulin formulation is a convenient treatment of patients with type 2 diabetes who are insulin-resistant and require high number of daily insulin injections. Compliance with insulin U-500 is higher that with non-concentrated insulins because of reduction in injection frequency to only 2 injections per day, its use a monotherapy, and decreased injection pain. Well-designed randomized trials are needed to study efficacy, safety, and overall cost of U-500 compared with other insulin modalities.

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