Review Article

HIGH-DOSE INSULIN THERAPY: IS IT TIME FOR U-500 INSULIN?

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ABSTRACT

Objective: To provide an overview of U-500 regular insulin action, review published clinical studies with U-500 regular insulin, and offer guidance to practicing endocrinologists for identifying patients for whom U-500 regular insulin may be appropriate.

Methods: This review has been produced through a synthesis of relevant published literature compiled via a literature search (MEDLINE search of the English-language literature published between January 1969, and July 2008, related to U-500, insulin resistance, concentrated insulin, high-dose insulin, insulin pharmacokinetics, and diabetes management) and the authors' collective clinical experience.

Results: The obesity epidemic is contributing to an increase in the prevalence of type 2 diabetes, as well as to increasing insulin requirements in insulin-treated patients. Many of these patients exhibit severe insulin resistance, manifested by daily insulin requirements of 200 units or greater or more than 2 units/kg. Delivering an appropriate insulin volume to these patients can be difficult and inconvenient and may be best accomplished with U-500 regular insulin by multiple daily injections or with continuous subcutaneous insulin infusion, rather than with standard U-100 insulin. Implementation of U-500 regular insulin in patients previously on other insulin formulations is described with a treatment algorithm covering dosage requirements ranging from 150 to more than 600 units per day on the basis of the authors' experience.

Conclusion: Regimen conversion of appropriately selected patients from high-dose, U-100 insulin to U-500 regular insulin therapy on the basis of the recommendations presented in this article may potentially result in improved glycemic control and lower cost. **(Endocr Pract. 2009;15:71-79)**

Abbreviations:
CSII = continuous subcutaneous insulin infusion; **DM** = diabetes mellitus; **HbA_{1c}** = hemoglobin A_{1c}; **NPH** = neutral protamine Hagedorn; **TZD** = thiazolidinedione; **UKPDS** = United Kingdom Prospective Diabetes Study

INTRODUCTION

U-500 regular insulin was first introduced into clinical practice in 1952. The original formulation, beef U-500 regular insulin (Eli Lilly and Company, Indianapolis, Indiana), was developed to address high insulin requirements of patients with type 1 diabetes mellitus (DM) or type 2 DM and severe insulin resistance caused by high levels of insulin antibodies to animal species insulins. This formulation was replaced by pork U-500 regular in 1980 and subsequently by U-500 regular human insulin (Humulin R U-500; Eli Lilly and Company, Indianapolis, Indiana) in 1997. Worldwide, Humulin R U-500 is now the only available formulation of insulin at a greater concentration than U-100 since withdrawal of Actrapid U-500 (Novo Nordisk, Bagsværd, Denmark) from the UK market in late 2007–early 2008.

Severe insulin resistance is encountered in clinical practice more commonly today than in the past. The most prevalent cause is obesity, which is an epidemic in the United States and worldwide (1), contributing not only to an increase in type 2 DM prevalence, but also to increas-

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ing insulin requirements in insulin-treated patients. Insulin resistance arising from elevated serum levels of insulin antibodies is now rare because of the use of highly purified and nonimmunogenic human insulins and analogues. New etiologies of severe insulin resistance include the use of protease inhibitors for human immunodeficiency virus and graft vs host disease after bone marrow transplantation, both of which may result in an acquired form of lipodystrophy (2,3). Finally, insulin receptor defects (type A insulin resistance syndromes) (4) and insulin receptor autoantibodies (type B insulin resistance syndrome) (5) remain rare causes of extreme insulin resistance.

In the past, the use of high-dose insulin was a source of clinical controversy (6). Twenty years ago, hyperinsulinemia was considered potentially atherogenic. This concern has been alleviated by numerous randomized controlled trials, such as the United Kingdom Prospective Diabetes Study (UKPDS) (7), concluding that exogenous hyperinsulinemia does not lead to increased risk of macrovascular disease. Endogenous hyperinsulinemia, however, is a marker for metabolic syndrome and its attendant increased cardiovascular risk (8). New data suggest that insulin is actually anti-inflammatory, at least when glucose levels are controlled (9). However, simply overcoming insulin resistance via high doses of insulin, without eliminating the caloric excess that contributed to it, has been questioned (10).

Delivering an appropriate volume of insulin to patients with severe insulin resistance can be difficult and may be best accomplished by using a more concentrated insulin preparation than standard U-100 insulin. When a given insulin dosage required for adequate glycemic control exceeds 100 units (or with current insulin pens, dosages exceeding 60 to 80 units), a 1-mL syringe (or single insulin pen) using U-100 insulin will not be large enough, leading to inconvenience and impracticality (ie, several injections per dose). Furthermore, the large injection volume and resultant large subcutaneous insulin depot may be painful for the patient (11-13). Finally, and perhaps most importantly, a large subcutaneous insulin depot may impede insulin absorption (14), reducing therapy effectiveness and resulting in persistent suboptimal glycemic control.

Frequency of use of U-500 regular insulin in the United States has recently increased remarkably (71% increase in vials per month prescribed from January 2007 through June 2008—up to 5720 vials per month [IMS Health, National Prescription Audit Monthly, July 2005-June 2008]), commensurate with the global twin epidemics of obesity and type 2 DM. The purpose of this review is to provide a comprehensive clinical update on this important option for the treatment of patients with type 2 DM (or occasionally type 1 DM) who have high insulin requirements. The recommendations presented here have been developed through critical assessment of the available literature (MEDLINE search of the English-language literature published between January 1969, and July 2008, related to U-500, insulin resistance, concentrated insulin, high-dose insulin, insulin pharmacokinetics, and diabetes management) combined with the clinical experience of the authors and may serve as a useful reference during management of U-500 insulin.

U-500 REGULAR INSULIN ACTION

Investigation of the differential effects of higher insulin concentrations on pharmacokinetic and glucodynamic profiles in humans has been quite limited. Studies by Binder et al demonstrated a decreased absorption rate of subcutaneously injected insulin with increasing insulin concentration or injection volume (14,15). Galloway et al observed no significant differences in peak or time-to-peak serum insulin concentrations between 0.25 unit/kg doses of U-40 up to U-500 pork regular insulin; however, time-to-peak blood glucose response was significantly slower with U-500 compared with U-40, U-80 (neutral regular), and U-100 concentrations (16). A possible explanation for the observed lack of difference in time-to-peak serum insulin concentrations between different insulin formulations in the Galloway et al study could be counterbalancing effects of concentration and volume on absorption rate. In other words, the increased concentration, coupled with the reduced volume of concentrated insulins may be offsetting, although this is controversial (17). Although limited by an atypical low-dosage regimen, a recent pharmacokinetic and glucodynamic study using 0.2 units/kg of human U-500 regular insulin in healthy, nonobese participants found time-to-onset within 30 minutes, with peak insulin levels at 1.75 to 4 hours (mean, approximately 3 hours); peak glucose infusion rate at 3.5 to 4.5 hours; and duration of action 6.5 to 10 hours after subcutaneous abdominal injection (18). Thus, human U-500 regular insulin appears to have a similar time-to-onset and slightly slower time-to-peak than U-100 human regular insulin and a duration of effect similar to human neutral protamine Hagedorn (NPH) insulin. Studies comparing intrasubject variability with identical dosages of U-500 vs U-100 regular human insulin and pharmacokinetic and glucodynamic studies in lean and obese type 2 diabetic patients using higher unit per kg dosages have not been performed.

CLINICAL STUDIES WITH U-500 REGULAR INSULIN

Table 1 summarizes the published clinical series (most retrospective and none randomized) of U-500 human regular insulin use in patients with primarily type 2 DM (11,12,19-24). We performed statistical analysis of these studies, comparing pre– and post–U-500 regular therapy results (Table 2). This analysis showed significant reductions in hemoglobin A_{1c} (HbA_{1c}) (weighted mean differ-

Table 1
Reported Clinical Series With U-500 Regular Insulin

Study No.	Study authors	Patients, No.	Study type	Diabetes type	Method of use	Follow-up duration, mo
1	Knee et al (11)	4	Retrospective	Type 2	CSII	6
2	Garg et al (19)	16	Retrospective	Type 1 and 2	MDI[a]	3 to 36 (mean 23)
3	Neal (20)	20	Retrospective	Type 2	TID	6
4	Wafa and Khan (21)	15	Retrospective	Type 2	SC	12
5	Lane (12)	9	Retrospective	Type 2	CSII	3
6	Ballani et al (22)	9	Prospective	Type 2	BID	6
7	Nayyar et al (23)	81	Retrospective	Type 1 and 2	SC/CSII[a]	1 to 98 (mean 30)
8	Bulchandani et al (24)	6	Retrospective	Type 2	CSII[a]	6

Abbreviations: BID, twice daily; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections per reference 12; SC, subcutaneous (frequency of injection unspecified); TID, three times daily.
[a] Actrapid U-500 (Novo Nordisk, Bagsværd, Denmark); other studies used Humulin Regular U-500 (Eli Lilly and Company, Indianapolis, Indiana).

ence, 1.60% [from 10.00% to 8.40%; P = <.001]) and increases in weight (weighted mean difference, 4.2 kg [from 118.8 kg to 123.0 kg; P = .002]). Nonsignificant increases in total insulin dose were observed in the 3 to 98 months after patients were switched to U-500 regular insulin administered either by subcutaneous injection or by continuous subcutaneous insulin infusion (CSII). This weight gain in relation to HbA_{1c} improvement is similar to that typically observed with U-100 insulin therapy (25). Concomitant use of various oral antihyperglycemic agents (mainly metformin plus thiazolidinediones [TZDs]) was reported in approximately 50% of U-500 regular–treated patients; such therapy is not approved by the US Food and Drug Administration because of lack of sufficient study. However, caution in combining TZDs with insulin is appropriate regarding congestive heart failure risk (26,27). Hypoglycemia, when reported, was rare (0 to 1 patient episodes per study period) (11,12,20,24) or infrequent (1 to 2 episodes per patient month, which was no different than before the start of U-500 regular insulin therapy) (21). No severe hypoglycemic episodes or related adverse events (including catheter occlusions) were reported when U-500 regular insulin was used in CSII. Garg et al reported that 4 of 6 patients were able to switch back to U-100 insulin after a mean of 14 months of treatment with U-500 regular insulin (Actrapid U-500, Novo Nordisk, Bagsværd, Denmark) (28).

IDENTIFICATION AND CLINICAL WORKUP OF POTENTIAL CANDIDATES FOR U-500 THERAPY

Box 1 lists conditions of the potential patients for concentrated insulin therapy who have severe insulin resistance. Severe insulin resistance has been defined as a total daily insulin requirement of 200 units or more in insulin-treated diabetic patients (32). It appears reasonable to additionally relate total daily insulin to body weight in all patients; we propose insulin dosages in excess of 2 units/kg per day as an alternative definition of severe insulin resistance. This definition has been used as an exclusionary criterion in a recent randomized controlled trial of intensive insulin therapy in type 2 diabetic patients with a body mass index of 45 kg/m^2 or less (33). In addition, some insulin-treated patients with type 2 DM may require U-500 regular insulin solely on the basis of obesity-related high insulin requirements, and high total insulin dosage is the usual reason clinicians decide to switch to U-500 insulin (see Implementation of U-500 Regular Insulin Therapy in the following text).

Evaluation of patients presenting with marked hyperglycemia and typical features of severe insulin resistance such as acanthosis nigricans, with or without severe obesity (34), includes ruling out of secondary causes such as Cushing syndrome, acromegaly, glucagonoma, and pheochromocytoma. Reviewing concentrations of fasting serum insulin, postprandial insulin, and C-peptide before treatment with insulin may be useful in the consideration of syndromic etiologies (35). Fasting adiponectin levels (recently reported to be elevated in patients with insulin receptor defects) (36), insulin receptor autoantibodies (5), leptin levels (characteristically less than 2.5 ng/mL in lipodystrophic diabetes) (37), and other genetic testing (4,34) may be obtained by specialists at tertiary referral centers like the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases. Most patients with syndromic forms of insulin resistance require more

Box 1
Conditions That May Qualify Patients as Potential Candidates for U-500 Regular Insulin Therapy

- Type 2 diabetes with obesity and/or severe insulin resistance (13,29,30)
- Type 2 diabetes requiring high-dose insulin (13,29,30)
- Postoperative or posttransplant state
- High-dose glucocorticoid or pressor therapy
- Severe systemic infection
- Gestational diabetes mellitus with severe insulin resistance (29-31)
- Defects of insulin action
- Lipodystrophic diabetes (congenital [2] and acquired [2,3])
- Type A insulin resistance syndromes (leprechaunism and Rabson-Mendenhall syndrome) (4,29,30)
- Rare forms of immune-mediated diabetes such as anti-insulin receptor antibodies (type B insulin resistance syndrome) (5,29,30)
- Others (4,29,30)

Table 2
Comparative Parameters Pre– and Post–U-500 Regular Therapy in Reported Series[a,b]

Study No.	Patients, No.	Pre HbA_{1c}, %	Post HbA_{1c}, %	Pre TDI, units	Post TDI, units	Pre weight, kg	Post weight, kg
1	4	10.8 (2.35)[c]	7.3 (1.34)[c]	333.8 (199.9)[c]	213.5 (47.2)[c]	…	…
2	16	11.34 (3.27)	8.97 (1.89)	313.8 (111.4)[d]	282.7 (151.6)[d]	112.7 (31)	119.2 (33.1)
3	20	9.59 (1.37)	7.83 (1.26)	221.6 (63.3)	214.7 (44.3)	124.8 (27.7)[d]	128.0 (28.8)[d]
4	15	9.8 (1.8)[d]	7.6 (1.4)[d]	219.3 (58.6)[d]	335 (115.5)[d]	126.6 (31.5)[d]	128.6 (31.7)[d]
5	9	8.8 (0.98)	7.67 (0.98)	171.9 (41.9)	166.6 (47.8)	120.28 (38.7)	122.17 (38.6)
6	9	10.3 (1.9)	7.8 (0.6)	289 (61)	322 (166)	109.9 (26)	114.6 (2.9)
7	81	10.1 (1.8)	8.9 (2.0)	311 (111.5)	368.4 (179.9)	116.2 (27.1)	121.3 (29.3)
8	6	9.1 (1.8)	6.9 (0.9)	391 (91)	296 (68)	142.0 (21.8)	139.2 (22.0)
		Weighted mean HbA_{1c}		Weighted mean TDI		Weighted mean weight	
		10.00	8.40	286.0	316.9	118.8[e]	123.0[e]
Weighted mean Δ (post-value minus pre-value)[f]		–1.60%		+30.9 units		+4.2 kg	
P value[g]		<.001		.17		.002	

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; TDI, total daily insulin.
[a] Data are presented as mean (standard deviation).
[b] See Table 1 for further information about studies 1 through 8.
[c] Standard deviations for mean values were calculated from individual patient data in published report.
[d] Additional data provided by written communications with respective authors (Ranjna Garg, MD, April 2008; J. Matthew Neal, MD, April 2008; Mukhtar I. Khan, MD, April 2008)
[e] Available data for these parameters were based on 156 participants.
[f] Weighted mean change was calculated from the study pair differences (post-value minus pre-value) weighted according to the study sample size.
[g] One-sample *t* test was used to determine whether the change was significant.

than 3 units/kg per day (ie, they have extreme insulin resistance) and are nonobese, with a body mass index less than 30 kg/m^2—often less than 25 kg/m^2 (Phillip Gorden, MD, oral communication, May 2008). Referral of such patients should not delay treatment with high-dose insulin therapy as appropriate. Detailed consideration of these various syndromic forms of diabetes is beyond the scope of this review (2,4,5,29,30,34).

PRESCRIBING CONSIDERATIONS FOR U-500 REGULAR INSULIN

When prescribing U-500 regular insulin, it is important to delineate the dose of insulin both by volume and by total (actual) units to avoid dosing errors. Some advocate use of a tuberculin syringe with the prescribed dose written by volume, although the smallest tuberculin syringe needle available in the United States is 27-gauge (13,30), and these syringes may have limited availability through some health care plans. U-500 regular insulin may also be administered with U-100 insulin syringes, which are less expensive and have finer needles (30 to 31 gauge), as long as the dose is concomitantly denoted by volume, "units" on the syringe, and actual insulin units, with frequency of dosing specified. For example, to prescribe a dose of 50 total units of insulin to be administered as U-500 regular insulin before meals, the prescription should be written as follows: "U-500 regular insulin: inject 50 units (0.1 mL or 10 units using a U-100 insulin syringe) 3 times daily before meals." These recommendations are consistent with those of The Institute of Safe Medical Practices (38). Use of 0.3-mL or 0.5-mL U-100 syringes may reduce the risk of inadvertent overdosage and severe hypoglycemia (13). Prescribing glucagon emergency kits for outpatients using U-500 regular insulin is prudent (39).

IMPLEMENTATION OF U-500 REGULAR INSULIN THERAPY

Compared with U-100 regular insulin, U-500 regular insulin has a time-action profile with an extended duration or "tail" (18). This extended action leads to U-500 regular insulin being dosed and administered differently than U-100 regular insulin when used alone or as part of basal-bolus therapy. Dosing of U-500 regular insulin can best be summarized according to total daily insulin requirements: daily dosages of 150 to 300 units/day; 300 to 600 units/day; and more than 600 units/day (Table 3). For all patients (whether on multiple daily injections or CSII), we feel it is prudent to empirically reduce the conversion dose by 10% to 20% if the baseline HbA_{1c} level is 8% or lower and increase the dose by 10% to 20% if the HbA_{1c} level is 10% or higher, given the trends reported in the published clinical series in more adequately insulinized vs underinsulinized patients (Tables 1 and 2). For patients with baseline HbA_{1c} levels between 8% and 10%, dose-for-dose conversion from U-100 is recommended. U-500 regular insulin should be administered at least 30 minutes before meals—the same as for U-100 regular insulin—because its time-to-onset of action is similar to that of U-100 regular insulin (18). Patients should regularly monitor blood glucose levels at home and follow guidelines for correcting premeal hyperglycemia (40), which if severe, might entail use of a high-dose, rapid-acting insulin analogue in addition to the U-500 insulin for faster correction according to prescribing physician judgment.

Dosages of 150 to 300 Units Daily

Patients with insulin requirements between 150 and 300 units per day have experienced improved glycemic control when U-500 regular insulin is used, either by itself (21-23) or in combination with basal insulin (41). When used without basal insulin, U-500 regular insulin can be split into 2 or 3 premeal doses. With twice-daily injections, we recommend 60% of the total daily dose be given before the morning meal and 40% be given before the evening meal (30). Ballani et al used 3 daily injections in patients with U-500 regular dosages ranging from 150 to 650 units (mean 322 units) (22). If administration of 3 daily injections is preferred, we recommend giving 40% to 45% of the total daily dose before the morning meal, 30% to 40% before the noon meal, and 20% to 30% before the evening meal (30). U-500 regular insulin may also be combined with basal insulin (glargine, detemir, or NPH) as the bolus component of basal-bolus therapy regimens, especially in patients switching from U-100 basal-bolus therapy regimens (40). In this case, the proportion of basal to bolus insulin would remain the same as before U-500 regular insulin therapy, with careful adjustment of the basal component as usual according to fasting blood glucose values.

Dosages of 300 to 600 Units Daily

For dosages of U-500 regular insulin between 300 to 600 units per day, we recommend 3 daily injections as described in the preceding text. If blood glucose values are consistently elevated in the morning, a fourth dose at bedtime may be cautiously added. We recommend administering most of the total daily insulin dose during the daytime with less at bedtime (ie, approximately 30% of total daily dose with each meal and not more than 10% at bedtime). Early morning (2 AM or 3 AM) glucose monitoring is prudent, especially with initiation of bedtime U-500 regular dosing. Alternatively, as mentioned in the previous section, basal-bolus therapy may be used, in which basal insulin provides overnight glycemic control. Since all basal insulins and analogues are available in only U-100 formulations, at total daily insulin requirements of 300 to 600 units, the basal dose almost always must be split and administered in 2 equal daily doses, given the large volume required. Basal-bolus therapy at these dosages may therefore involve 5 or more subcutaneous injections daily, potentially pushing the consideration of conversion to CSII.

Dosages Greater Than 600 Units Daily

For dosages of U-500 regular insulin greater than 600 units daily, we recommend exclusively using 4 daily injections of U-500 regular insulin (30). As mentioned, basal-bolus therapy may be impractical at these doses due to the volume of basal insulin required and the number of

Table 3
U-500 Regular Insulin Dosing Algorithm[a]

Required daily insulin dose, units	Options for U-500 regular insulin therapy (injection frequency, schedule, delivery method)[b]	U-500 regular insulin dosage distribution guide (based on percentage of total daily dose)[c,d]
	2 daily injections (eg, 8 AM, 6 PM) with or without basal insulin[e]	AM injection = 60% total daily insulin PM injection = 40% total daily insulin (ie, 60/40)
	3 daily injections (eg, 8 AM, noon, 6 PM) with or without basal insulin[e]	40/30/30 or 45/35/20 or 40/40/20
150 to 300	CSII (1 "pump unit" = 0.01 mL = 5 units U-500 regular insulin)	3 mealtime boluses + 24-hour basal insulin infusion (eg, for basal rate = 50% total daily insulin, mealtime boluses should be distributed as 20/15/15; or for basal rate = 20% of total daily insulin, mealtime boluses should be 30/25/25)
	3 daily injections with or without basal insulin[e]	As above
300 to 600	4 daily injections (eg, 8 AM, noon, 5 PM, 10 PM)	30/30/30/10
	CSII	As above
>600	4 daily injections	25/25/25/25 or 30/30/30/10

Abbreviation: CSII, continuous subcutaneous insulin infusion.
[a] Proposed algorithm for dosing conversion to U-500 regular insulin therapy on the basis of a patient's previous total daily insulin requirements (adapted from Cochran et al [29,30]).
[b] U-500 regular boluses recommended at least 30 minutes premeal; dosage titration is according to frequent self-monitored blood glucose measurement.
[c] Empirically reduce the conversion dose from U-100 by 10% to 20% if baseline hemoglobin A_{1c} level is 8% or lower and increase the dose by 10% to 20% if the hemoglobin A_{1c} level is 10% or higher.
[d] Boluses according to proportion of carbohydrates with meal or carbohydrate counting according to patient preference and physician judgment.
[e] Basal insulin refers to glargine, detemir, or neutral protamine Hagedorn (see text section Implementation of U-500 Regular Insulin Therapy, subsection Dosages of 150 to 300 Units Daily).

injections, and CSII is not suited to greater than 15 units per hour basal rates using the U-500 regular formulation. Doses can be evenly divided, but if morning hypoglycemia is an issue, the bedtime dose should be reduced. The only patients who are likely to require total daily dosages greater than 2000 units are those with syndromic insulin resistance etiologies (Box 1).

CSII THERAPY (FOR U-500 REGULAR DOSAGES GREATER THAN 600 UNITS DAILY)

Patients whose blood glucose levels remain uncontrolled with U-500 regular insulin–based multiple daily injection or basal-bolus therapy regimens may be able to achieve better glycemic control by switching to U-500 regular insulin via CSII (not an approved indication by US Food and Drug Administration). Also, patients with good glycemic control treated with U-500 regular by subcutaneous injections may switch to CSII from a multiple daily injection regimen on the basis on personal preference and affordability. For patients on CSII with high basal U-100 insulin infusion requirements (3 or more units per hour), switching to U-500 regular insulin infusion will avoid the need for inconvenient and costly pump cartridge (current reservoirs are 1.78 to 3.0 mL) and infusion set changes at intervals less than 1 to 2 days (11,12).

For patients already using U-500 regular insulin by multiple daily injections, this conversion is made by taking 50% of the total daily insulin dosage, dividing by 24, and administering this dose as a single basal hourly infusion rate via insulin pump with the other 50% distributed as premeal boluses (see Table 3). If the 24-hour insulin

requirement is determined based on U-100 insulin dosing, an additional calculation step of dividing this amount first by 5, then dividing again by 24, will yield the starting hourly insulin infusion rate for U-500 regular insulin by CSII in "pump units." No current commercial pumps have software for expressing insulin units if U-500 regular is being used. Initially, the night basal rate may be reduced slightly beginning at 10 PM to midnight and combined with 2 AM to 3 AM self-monitored blood glucose measurements to avoid nocturnal hypoglycemia. The use of real-time continuous glucose sensors may also be helpful for these patients (42).

Mealtime and correction doses of insulin are administered as boluses of U-500 regular insulin via insulin pump. Frequent changes in basal rates should be minimized because the pharmacokinetic and glucodynamic characteristics of U-500 regular insulin may cause a delayed effect. Additionally, changes to the basal rate should be initiated approximately 2 hours before the desired time of glycemic effect. For example, if an effect on the blood glucose is desired from 8 AM to 8 PM, the pump should be programmed to achieve the desired effect from 6 AM to 6 PM. Bolus dosing should be based on carbohydrate intake or carbohydrate counting by the patient. Correction boluses and insulin to carbohydrate ratios may be set in U-500 "pump units" (ie, 20% of actual units). Patients should be instructed to not bolus more frequently than every 4 to 6 hours to avoid overdosing and "stacking" of insulin doses. A more complete discussion of initiation of U-500 regular insulin by CSII is described elsewhere (11,12,24).

CONSIDERATION OF BARIATRIC PROCEDURES

Bariatric surgery has been reported to achieve resolution of type 2 DM in 76.8% of patients in a recent meta-analysis of all types of bariatric procedures. An 83.7% resolution rate has been documented with gastric bypass (43). Two clinical series reported that patients were able to discontinue U-500 regular high-dose insulin therapy after bariatric surgery (23,28). This may reflect reversal of glucotoxicity and/or lipotoxicity and significant improvement in β-cell function. It appears reasonable that patients who require high-dose U-500 regular insulin therapy be considered for bariatric surgery (assuming body mass index is 35 kg/m^2 or higher according to 1998 National Institutes of Health/National Heart, Lung, and Blood Institute guidelines) (44).

HOSPITAL USE OF U-500 REGULAR INSULIN

During hospitalization, the insulin requirements of patients already using U-500 regular insulin may become greater, owing to the stress of their illness. It is therefore useful to continue U-500 regular insulin in this population during hospitalization unless the medical situation calls for intravenous insulin infusion, in which case U-100 regular insulin should be used. Formulary inclusion of U-500 regular in most hospitals requires a specific written and/or electronic policy with appropriate in-service instruction for the nursing staff. A dosage conversion chart, such as the one shown in Table 4, converting between volume U-100 syringe "units" and actual U-500 regular units, should be placed in a prominent place on the patient's hospital record and may also be useful in the outpatient setting. "U-500 regular insulin" should be highlighted in both the hospital chart and medication administration record according to each hospital's policy. Many hospitals favor use of volumetric tuberculin syringes (with needle guards) for inpatients, which forces prescribing by volume and actual units. Storage of U-500 regular insulin with clear and unambiguous labeling and dispensing and administration separate from U-100 insulin are crucial.

ECONOMIC CONSIDERATIONS WITH USE OF U-500 REGULAR INSULIN

Previous reviews of U-500 regular insulin use have described the cost-effectiveness of U-500 regular insulin (13,29,30). In the setting of CSII use, Knee et al estimated a potential cost savings of $2600 per year for insulin and $3400 per year for insulin pump supplies on the basis of 2002 average wholesale prices (11). This does not include reduced battery costs since infusing one-fifth the volume lengthens battery life. Because U-500 regular insulin is actually less expensive on a unit for unit basis than U-100 insulin (each 20 mL vial of U-500 regular contains 10000 units vs 1000 units per U-100 insulin vial), U-500 regular insulin should be at least an equal tier and copayment for insured patients. Patients taking fewer than 300 units of U-500 regular insulin daily will have some insulin wastage given the 28-day shelf life of U-500 regular insulin after opening; CSII–treated patients can fill the cartridge to meet anticipated 3-day insulin needs.

The cost of medications and supplies constitutes only 12% of direct medical expenditures for diabetes in the United States (45); the greatest costs are related to medical care for chronic complications including hospitalization and indirect costs related to reduced productivity in the work place and premature mortality. Data from the UKPDS have demonstrated a correlation between sustained HbA_{1c} reduction and reduced risk of microvascular complications (1% reduction in HbA_{1c} = 28% to 37% reduction in microvascular complications) in patients with type 2 DM (7,46). Although no prospective studies have evaluated the effect of U-500 regular insulin therapy on development of diabetes complications, the average 1.60% reduction in HbA_{1c} observed across reported U-500 regular series (Table 2), if sustained, could potentially translate into a significant reduction in microvascular complications. If achieved, such a reduction in complications would result in marked cost savings and favorable effect on patients' lives.

Table 4
Chart for Calculating the U-500 Regular Insulin Dose When Using a Tuberculin Syringe or a U-100 Syringe[a]

Volume, tuberculin syringe (mL)	U-100 syringe ("units")	U-500 regular insulin dose (actual units)
0.1	10	50
0.2	20	100
0.3	30	150
0.4	40	200
0.5	50	250
0.6	60	300
0.7	70	350
0.8	80	400
0.9	90	450
1.0	100	500

[a] This conversion chart may be useful in both the outpatient and inpatient settings.

CONCLUSION

Since the introduction of U-500 regular insulin in 1952, increasing needs for concentrated insulin therapy have emerged. Many patients who have type 2 DM with obesity and severe insulin resistance have poor glycemic control with conventional U-100 insulin therapy. U-500 regular insulin may provide these patients with improved glycemic control with smaller injection volumes and potentially fewer injections than that required with U-100 insulin. Additional benefits to the patient on CSII using U-500 regular insulin include increased convenience by reducing the frequency of cartridge changes and the possibility of improved insulin absorption compared with absorption with subcutaneous multiple daily injections. Because of potential confusion associated with dosing of U-500 regular, it is important for physicians, nurse educators, hospitals, pharmacists, and patients to be familiar with the conversion of doses between U-100 insulin and U-500 regular insulin, administered either by U-100 insulin syringe, tuberculin syringe, or insulin pump. U-500 regular insulin therapy requires close monitoring of blood glucose levels by the patient and physician with subsequent careful titration to glycemic targets. U-500 regular insulin is an important therapeutic option for patients with severe insulin resistance who require high-dose insulin therapy.

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