Use of U-500 Regular Insulin via Continuous Subcutaneous Insulin Infusion: Clinical Practice Experience

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Despite current available therapies, patients with severe insulin resistance and large insulin requirements present challenges in achieving good glycemic control. Use of U-500 regular insulin (U-500R), which is five-fold concentrated, can reduce the number of injections required, insulin volume, discomfort, and possibly improve absorption rates. It has an onset similar to U-100 regular insulin and a duration similar to U-100 neutral protamine Hagedorn.[1] U-500R subcutaneous injections can significantly reduce hemoglobin A1c (HbA1c).[2] Its use via continuous subcutaneous insulin infusion (CSII) has been reported up to 12 months. This was associated with HbA1c reduction between 1.2% and 3.5%, weight gain, no change in total daily dose (TDD) of insulin, infrequent hypoglycemia, increased patient satisfaction, and cost savings.[3–5]

In our work, we retrospectively reviewed medical records of 10 patients in our practices who have used U-500R via CSII, followed for up to 92 months. Their data are shown in **Table 1**. Values are presented as mean ± standard deviation where applicable. Paired *t*-test was used to analyze changes from baseline. Their mean age was 45.5 ± 10.9 years. Eight patients had type 2 diabetes, one started the treatment during pregnancy, two had associated nonalcoholic steatohepatitis, and two had type 1 diabetes. Patients were obese with baseline weight of 108.5 ± 15.4 kg and body mass index of 35.9 ± 5.1 kg/m^2. The TDD was 234 ± 111 U of U-100 insulin/day (2.2 ± 0.9 U/kg/day). Mean baseline HbA1c was 9.0 ± 1.1% (6.6–10.9%). Seven patients were on multiple daily U-100 insulin injections, and three were on insulin lispro via CSII. Additionally, five were using metformin, thiazolidinediones, and/or a glucagon-like peptide-1 agonist.

The duration of U-500R via CSII use was 31.8 ± 28.1 months (range 6–92), with five patients using longer than 12 months. After the treatment started, HbA1c (%) was 7.3 ± 0.8 ($p = .01$), 7.5 ± 1.0 ($p < .01$), and 7.7 ± 0.7 ($p = .02$) at 3, 6, and 12 months. Hemoglobin A1c at the end of the follow-up period was 7.3 ± 0.6%, reflecting a reduction of 1.6 ± 1.3% ($p < .01$). Hemoglobin A1c decreased in nine patients, and final levels were <8.0% in nine patients. Two of three patients who previously used lispro via CSII had HbA1c reduction, and the other remained stable. Body weight increased significantly starting at 6 months with a mean of 8.9 ± 8.7 kg or 7.5 ± 6.7% at the end of the follow-up. There were no significant changes in TDD. Other diabetes medications, except metformin, were discontinued. Most patients used a Minimed; patients 5 and 9 used an Animas.

Hypoglycemia was not increased, except for the pregnant patient who experienced morning hypoglycemia, likely from daytime insulin stacking and overnight fasting, requiring an overnight basal rate suspension. The patient had elevated postprandial glucose levels, which resolved after bolusing insulin 60 minutes before meals as previously recommended.[3,6]

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Abbreviations: (CSII) continuous subcutaneous insulin infusion, (HbA1c) hemoglobin A1c, (TDD) total daily dose, (U-500R) U-500 regular insulin

Keywords: continuous subcutaneous insulin infusion, insulin pump, insulin resistance, U-500 regular insulin

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Table 1.
Patients' History and Detail of U-500R via Continuous Subcutaneous Insulin Infusion Use

Patient	Age/sex	Diabetes history	Diabetes treatment at baseline	Duration of therapy (months)	Baseline TDD (U-100 units/day)	Baseline HbA1c (%)	6 months HbA1c (%)	Last HbA1c (%)	Last TDD (U-100 U/day)
1	45/female	Type 1	Lispro via CSII, metformin	12	122	6.6	Not available	7.2	123
2	23/male	Type 1	Lispro via CSII	92	135	9.2	7.7	6.3	168
3	35/female	Type 2, pregnant	Lispro via CSII	12	225	8.2	7.5	7.1	200
4	50/female	Type 2, NASH	Glargine, aspart, metformin, pioglitazone	6[a]	200	10.9	7.0	7.0	160
5	58/female	Type 2	Glargine, lispro	12	260	9.2	8.1	7.7	361
6	55/male	Type 2	Glargine, lispro	12	260	10.2	9.2	7.8	387
7	37/female	Type 2	Glargine, lispro, metformin, rosiglitazone, exenatide	24[b]	250	9.0	6.5	7.0	240
8	53/male	Type 2	Glargine, metformin, rosiglitazone, exenatide	36	520	8.8	8.0	7.4	335
9	45/male	Type 2	Glargine, aspart	52	180	9.1	8.0	8.7	185
10	53/male	Type 2, NASH	Glargine, lispro, mixed 75/25, pioglitazone	60	190	9.0	5.8	7.6	200
Mean ± standard deviation				31.8 ± 28.1	234 ± 111	9.0 ± 1.1	7.5 ± 1.0[c]	7.3 ± 0.6[c]	235 ± 93[d]

NASH, nonalcoholic steatohepatitis.
[a] Underwent Roux-en Y gastric bypass with resolution of diabetes.
[b] Discontinued U-500R CSII because of personal reasons.
[c] *P* value < .01 compared to baseline.
[d] *P* value = .96 compared to baseline.

Two patients discontinued the treatment: one because of bariatric surgery with resolution of diabetes and one because of personal reasons. One patient discontinued temporarily because of a warning regarding possible accidental insulin delivery during pump priming, causing hypoglycemia. However, diabetes control worsened, and the treatment was restarted. Eight of nine remaining diabetes patients continue to be on the treatment.

We conclude that U-500R via CSII is safe and effective in achieving long-term glycemic control in diabetes patients with severe insulin resistance.

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