MIFEPRISTONE DECREASED THE USE OF CONCENTRATED U500 INSULIN IN PATIENTS WITH ENDOGENOUS HYPERCORTISOLISM WHO HAVE TYPE 2 DIABETES MELLITUS

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INTRODUCTION

- Excess cortisol contributes to insulin resistance and complicates the treatment of type 2 diabetes mellitus (T2DM)[1-3]
- Mifepristone (Korlym®, Corcept Therapeutics) is a competitive glucocorticoid receptor antagonist shown to improve insulin sensitivity and can lead to reduction or elimination of medicines used to help control hyperglycemia[4]
- We previously reported results of screening in a private practice that found that 60% of patients using concentrated U500 insulin (U500; Humulin® R U-500, Eli Lilly) had at least 1 positive biochemical test for hypercortisolism[5]
- We now report the results of medical therapy with mifepristone in a cohort of 14 patients who refused surgery or were not candidates for surgery

CASE PRESENTATIONS AND RESULTS

- Fourteen patients (7 men, 7 women) with hypercortisolism—demonstrated by at least 1 positive test (1-mg overnight dexamethasone suppression test [DST] cortisol ≥1.8 µg/dL or late night salivary cortisol [LNSC] ≥0.145)—had an average cortisol of 2.26 µg/dL after a DST
- Patient characteristics are shown in **Table 1**, and results of biochemical tests and subsequent testing are shown in **Table 2**
- Patients were started on mifepristone (300 mg/day), then titrated after 2 weeks based on tolerability and response
- Mifepristone therapy was discontinued in 2 patients after 3 months because of cortisol withdrawal symptoms, and the mifepristone dosage was limited to 300 to 600 mg/day in 3 patients with chronic renal disease
- At 6 months, most patients were on 600 mg (average dose 587.5 mg/day)
- Compared with baseline, mifepristone treatment resulted in a 1% reduction in HbA1c and 43% reduction in the average daily dosage of insulin at 3 months, and a 1% reduction in HbA1c and 41% reduction in insulin at 6 months (**Figure 1**)
- At 6 months, patients experienced a statistically significant reduction (P <0.01) in insulin, although the change in HbA1c was not statistically significant

Table 1. Baseline Characteristics*

Sex, M/F	7/7
Age, yrs	64 (36-73)
Weight, kg	273 (177.8-442.2)
Body mass index (BMI), kg/m²	40.4 (31.5-83.5)
Duration of T2DM, yrs	15 (6-29)
Hypertension, n	14
Hyperlipidemia, n	14
Chronic renal disease, n	3
Osteoporosis, n	3
Coronary artery disease, n	3
HbA1c, %	8.6 ± 0.4
Fasting Blood Glucose, mg/dL	184.5 ± 14.9
U500 insulin total daily dose, IU/day	250 (50-450)
GLP-1, n	11
SGLT-2, n	7
Metformin, n	6
Thiazolidinediones, n	2
DPP-4 Inhibitor, n	1

*Data presented as median (range), or mean ± standard error of the mean

DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; HbA1c = glycated hemoglobin; SGLT-2 = sodium-glucose cotransporter 2.

Table 2. Results of Cortisol/ACTH Testing and Imaging

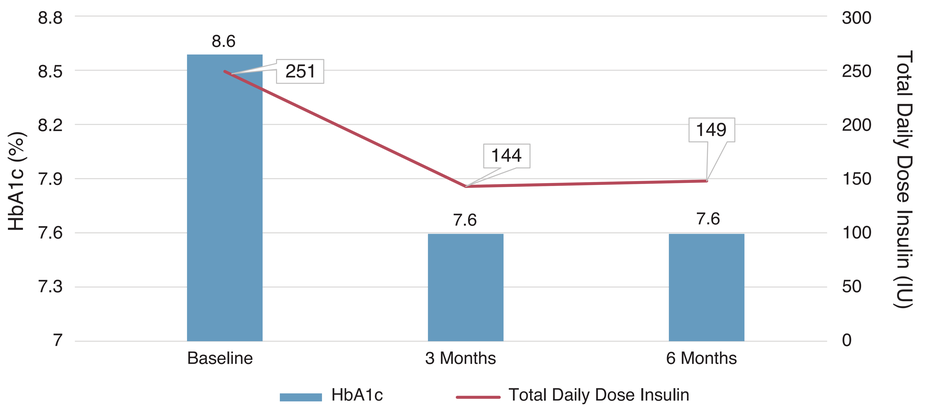
Patient No.	Sex (M/F)	Age (yrs)	DST* (µg/dL)	LNSC (positive/total)	UFC (µg/24h)	ACTH** (pg/mL)	Imaging Source
1	M	61	2	1/3	27	10.1	NVS
2	M	73	1.6	0/3	6	3.8	UAH
3	F	67	2.1	0/3	8	4.1	UAH
4	F	36	1.2	1/3	21	3.3	NVS
5	F	69	5	1/3	4	4.3	UAH
6	F	70	1.2	1/2	6	5.6	UAH
7	M	64	1.5	0/3	23	3.7	UAA: 0.7 cm
8	M	66	1.7	3/3	12	3.3	UAH
9	M	46	1.1	2/3	3	3.2	NVS
10	M	60	1.7	0/0	222	2.6	UAA: 0.5 cm
11	F	64	3	0/0	11	5.9	UAH
12	F	55	2.3	0/1	<2	4.1	NVS
13	M	58	4.1	0/4	4	9.5	UAA
14	F	70	3.1	1/3	63	8.1	BAA: 1.2 + 1.3 cm

*Overnight DST (normal <1.8 µg/dL); average = 2.26

**Post 1-mg dexamethasone-suppressed ACTH (normal <10 pg/mL)

ACTH = adrenocorticotropin hormone; BAA = bilateral adrenal adenomas; DST = dexamethasone suppression test; LNSC = late night salivary cortisol (normal ≤0.145 µg/dL); NVS = no source visible; UAA = unilateral adrenal adenomas; UAH = unilateral adrenal hyperplasia; UFC = 24h urinary free cortisol (normal ≤45 µg/24h).

Figure 1. Mifepristone-Induced Changes in HbA1c and U500 Insulin Use



HbA1c = glycated hemoglobin.

CONCLUSIONS

- It is important to identify underlying hypercortisolism in patients with diabetes who have severe insulin resistance requiring the use of U500
- Mifepristone treatment of patients with diabetes who required U500 and were subsequently found to have hypercortisolism resulted in a significant reduction in insulin and improved glycemic control

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DISCLOSURES

JWM: Consultant and speaker, Corcept Therapeutics.
JJS: Employee, Corcept Therapeutics.