Rapid Reversal of Acute Psychosis in the Cushing Syndrome with the Cortisol-Receptor Antagonist Mifepristone (RU 486)

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Annals of Internal Medicine. 1991;**114**:143-144.

The progesterone-receptor antagonist, RU 486 (mifepristone), is also, at higher concentrations, an effective antagonist of glucocorticoid action in vitro and in vivo (1-3). In normal humans, RU 486 blocks glucocorticoid negative feedback at the hypothalamic-pituitary level, inducing a compensatory increase in plasma adrenocorticotropin (ACTH) and cortisol levels (4, 5). In previous studies, patients with the Cushing syndrome caused by

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Table 1. *Serum Cortisol Levels in the Two Study Patients*

Patient	Serum Cortisol*		
	Before Treatment	During o,p'-DDD Therapy†	During Therapy with o,p'-DDD and RU 486
	← nmol/L →		
1‡	2000–2500	1800–2200	1800–2200
2§	1000–1500	800–1100	800–1100

* Normal level at 0800 hours is less than 450 nmol/L.
† o,p'-DDD = 1,1-dichlorophenyldichloroethane (mitotane).
‡ Male; age, 43 years.
§ Female; age, 32 years.

ectopic ACTH secretion or by adrenocortical carcinomas who received therapy with RU 486 (5 to 22 mg/kg body weight per day) showed clinical improvement, and no compensatory increases in plasma ACTH or cortisol levels were noted, probably because of ongoing hypothalamic and corticotroph suppression (6-8). In our study, RU 486 had a rapid, beneficial effect in reversing acute psychosis and preventing further psychiatric symptoms in two patients with inoperable end-stage cortisol-secreting adrenal cancers.

Case Reports

Patient 1, a 43-year-old man, had inoperable left-sided adrenal cancer with extensive metastases to the liver and lungs. Very high circulating cortisol (Table 1) and undetectable ACTH levels confirmed the clinical diagnosis of the Cushing syndrome. After receiving therapy with o,p'-DDD (1,1-dichlorodiphenyldichloroethane; mitotane) for 2 weeks (12 g/d; body weight, 74 kg), his mental state deteriorated acutely. Different psychiatric states were observed during a period of 8 to 12 hours; these included consecutively severe clouding of consciousness, mutism, and psychosis with nihilistic delusions. The patient's behavior was unpredictable, and he was considered to be at high risk for suicide. Psychiatric symptoms improved within 12 hours after 800 mg of RU 486 was administered, and all mental abnormalities disappeared within 24 hours. Therapy with RU 486 (800 mg daily) was continued but after 5 days hypoglycemic episodes occurred and eosinophilia reappeared. The daily dose of RU 486 was lowered to 400 mg without side effects. The patient died 2 weeks later from renal insufficiency caused by tumor obstruction of the inferior vena cava. Plasma cortisol levels remained elevated and unchanged until death, but no psychiatric symptoms recurred. Other signs and symptoms of the Cushing syndrome had started to subside.

Patient 2, a 32-year-old woman, also developed the Cushing syndrome because of an inoperable left-sided adrenal cancer with metastases to the liver and lungs. Her circulating cortisol level remained elevated (Table 1) and her ACTH level undetectable after 7 weeks of therapy with o,p'-DDD (8 g/d; body weight, 52 kg). She was admitted with rapidly developing signs and symptoms of paranoid psychosis, including depression, agitation, and hallucinations. Treatment with RU 486 (400 mg/d) resulted in improvement within 24 hours, with the complete disappearance of psychiatric symptoms within 3 days. These symptoms did not recur during the last 2 months of her life. Cortisol levels remained unchanged, and no evidence of relative adrenal insufficiency (hypoglycemia or eosinophilia) was observed. Other signs and symptoms of the Cushing syndrome decreased during this period.

Discussion

Patients with the Cushing syndrome show a wide range of mental abnormalities. Depression, often of a psychotic nature, is the most frequent symptom and is accompanied by a high risk for suicide (9). These symptoms of psychosis are difficult to treat and in most instances do not respond to antipsychotic drugs (9).

It has been previously reported that RU 486 results in clinical and biochemical improvement of patients with the Cushing syndrome (6-8). We found that RU 486 was probably useful in rapidly reversing the severe acute psychiatric symptoms in two patients with end-stage metastatic adrenal cancers. We chose a dose of 400 to 800 mg/d of RU 486 on empiric grounds. There is currently no way to distinguish between adequate or excessive blockade of glucocorticoid action, making the recognition of adrenal insufficiency in these patients difficult (10).

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