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Successful Treatment of Cushing's Syndrome with the Glucocorticoid Antagonist RU 486*

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ABSTRACT. A patient with Cushing's syndrome due to ectopic ACTH secretion was treated successfully with the new glucocorticoid antagonist RU 486 [17β-hydroxy-11β-(4-dimethylamino phenyl)17α-(1-propynyl)estra-4,9-dien-3-one]. This compound is a 19-nor steroid with substitutions at positions C11 and C17 which antagonizes cortisol action competitively at the receptor level. Oral RU 486 was given in increasing doses of 5, 10, 15, and 20 mg/kg·day for a 9-week period. Treatment efficacy was monitored by assessment of clinical status and by measuring several glucocorticoid-sensitive variables, including fasting blood sugar, blood sugar 120 min after oral glucose administration, and plasma concentrations of TSH, corticosteroid-binding globulin, LH, testosterone-estradiol-binding globulin, and total and free testosterone. With therapy, the somatic features of Cushing's syndrome (buffalo hump, central obesity, and moon facies) ameliorated, mean arterial blood pressure normalized, suicidal depression resolved, and libido returned. All biochemical glucocorticoid-sensitive parameters normalized. No side-effects of drug toxicity were observed. We conclude that RU 486 may provide a safe, well tolerated, and effective medical treatment for hypercortisolism. (*J Clin Endocrinol Metab* **61:** 536, 1985)

THE CURRENTLY available treatments for Cushing's syndrome caused by metastatic ACTH-producing tumors or adrenal cancer are often unsatisfactory. Surgical resection of the tumor, when feasible, may be only partially or temporarily effective in controlling Cushing's syndrome. Medical therapy with adrenolytic agents (*o,p'*-DDD) or steroidogenic enzyme inhibitors (aminoglutethimide or metyrapone) is frequently associated with toxic side-effects (1–5).

A clinically applicable glucocorticoid antagonist is, in theory, an attractive alternative treatment for hypercortisolism and has been sought for many years (6). The recently discovered compound RU 486 [17β-hydroxy-11β-(4-dimethylamino phenyl)17α-(1-propynyl)estra-4,9-dien-3-one], a 19-nor steroid with a high affinity for the rat glucocorticoid receptor with no agonist effects *in vitro* or *in vivo*, is a potent competitive glucocorticoid antagonist in rodents (7), nonhuman primates (8, 9), and man (10–12).

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We report here the successful treatment with RU 486 of a 25-yr-old man with Cushing's syndrome caused by the ectopic secretion of ACTH. During therapy, the somatic features of Cushing's syndrome (cervical fat pad, central obesity, and moon facies) improved, suicidal depression cleared, and glucocorticoid-sensitive measures, such as elevated fasting and postabsorptive blood sugar, normalized. The drug was tolerated well, and no side-effects were noted during therapy or after its discontinuation.

Case Report

The patient was in excellent health until the fall of 1981 when he noted loss of strength, short term memory, and attention span. In the spring of 1982, because these symptoms worsened, he discontinued his weight-lifting regimen. He complained of increasing anxiety and depression. In September 1982, he stopped working because of these cognitive and psychological changes. Treatment with antidepressants was initiated. His depression deepened, however, and led to two suicide attempts. At that time, he had moon facies, hypertension, and diabetes, and was evaluated for Cushing's syndrome. Both serum and urinary cortisol levels were elevated, and 17-hydroxycorticosteroid excretion increased during a standard 2- and 8-mg dexamethasone suppression test (13).

An intrathoracic mass lesion was found and was resected in

March 1983. The lesion was not contiguous with a bronchus. Microscopic and immunohistochemical examination of the specimen showed a carcinoid tumor with granules that stained with anti-ACTH serum. Immediately after surgery, plasma cortisol levels were normal. Insulin and antihypertensive and antidepressant medications were discontinued, and the patient's symptoms improved. By May 1983, however, his symptoms recurred, and his urinary cortisol excretion rate was about 500 μg/day. He was given metyrapone, but had only transient clinical improvement.

In August 1983, he was admitted to the NIH. He complained of disorientation, diminished memory and cognitive ability, impotence, a 20-lb weight gain over 3 yr, and long-standing muscle weakness. He had a ruddy round face. His blood pressure was 180/120 mm Hg, and his pulse was 90 beats/min. He was anxious and depressed. He performed calculations slowly. The thoracotomy scar was hyperpigmented. Computerized axial tomograms of the chest revealed multiple lung nodules. He had hypokalemic alkalosis (serum potassium, 1.9 meq/liter; bicarbonate, 38 meq/liter; chloride, 94 meq/liter; sodium, 147 meq/liter).

His medications, including maprotiline hydrochloride (Ludiomil), trifloroperazine (Stelazine), benztropin mesylate (Cogentin), and metyrapone (1 g/day) were stopped before laboratory evaluation. He became withdrawn, severely depressed, and complained that he felt unable to think clearly. Ludiomil was reinitiated because of suicidal ideation, and his depressive symptoms and cognition improved. Potassium supplements were given (20–120 meq/day). Treatment with increasing doses of RU 486 for 9 weeks caused marked improvement in all biochemical and clinical parameters of hypercortisolism (see *Results*).

Materials and Methods

Protocol

The protocol for the therapeutic use of RU 486 was approved under an investigational exemption for new drugs by the National Center for Drugs and Biologics, DHHS, and by the NICHHD Clinical Research Committee (83-CH-87). The patient participated in the study after giving informed consent. All tests were performed at the NIH Clinical Center.

RU 486 was formulated into 50-mg tablets by Roussel-UCLAF (Paris, France). A single oral dose of 6 mg/kg RU 486 given at midnight has been found to prevent morning adrenal suppression caused by 1 mg dexamethasone (11). Accordingly, the initial oral daily dose was 5 mg/kg and increased in 5 mg/kg increments every 1 or 2 weeks to a maximum of 20 mg/kg·day (see Fig. 1).

A number of clinical and biochemical glucocorticoid-sensitive measures were monitored to evaluate treatment efficacy. Clinical measures included blood pressure and body weight. The patient's mood was assessed daily by a self-report questionnaire and three times a week by psychiatric interviews (14). Metabolic and hormone measures included urinary excretion of nitrogen and fasting and postabsorptive blood sugar, which are elevated by hypercortisolism, and plasma concentrations of corticosteroid-binding globulin (CBG) (15), testosterone-estradiol-binding globulin (TeBG), testosterone (16, 17), LH (16, 17), and TSH (18, 19), which are suppressed by hypercortisolism.

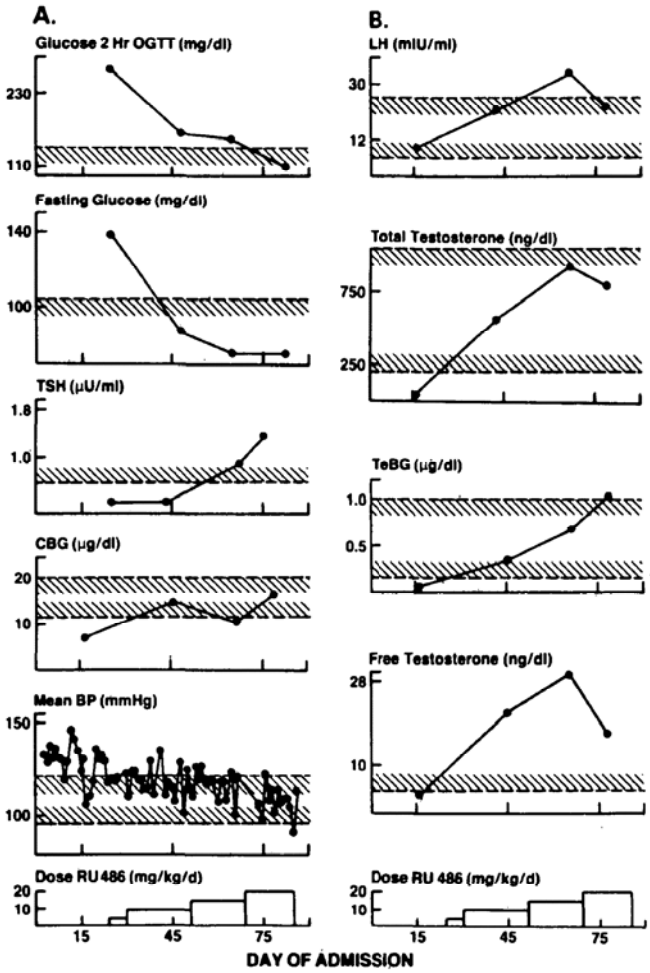

FIG. 1. The effect of RU 486 treatment on glucocorticoid-sensitive variables. A, Two hour post-OGTT (oral glucose tolerance test) and fasting blood sugar levels were elevated before RU 486 therapy and fell to normal levels during treatment. The serum TSH concentration was initially subnormal and rose progressively. CBG concentrations also rose into the normal range. Mean daily blood pressure decreased during RU 486 therapy. B, Plasma concentrations of LH, total testosterone, and free testosterone were initally depressed; all normalized with RU 486 therapy. TeBG capacity showed similar increases. *Shaded areas* represent the upper (▨) or lower (▨) normal range.

Plasma ACTH and plasma and urinary cortisol levels also were measured frequently. Metabolic and hormonal measurements were made on one to three morning blood samples drawn before therapy and during the final week of each dose interval. Standard oral glucose tolerance tests were performed after 3 days of ingestion of a 100-g carbohydrate diet using a 100-g glucose challenge. Creatinine, blood urea nitrogen (BUN), serum glutamic oxaloacetic acid-transaminase (SGOT), and serum glutamic pyruvic acid-transaminase (SGPT) measurements were monitored throughout treatment as indices of drug toxicity. Serial electrocardiograms and chest x-rays were done for a similar purpose.

Assays

Plasma testosterone (20), LH (21), ACTH (22), steroid biosynthetic intermediates (pregnenolone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, and 11-deoxycortisol) (20, 23), plasma and urinary cortisol (23), and serum TSH (24) were measured by RIA as previously described. CBG and TeBG were measured using a solid phase Concanavalin A-Sepharose assay (25). The free testosterone concentration was calculated from the measured levels of total hormone and binding proteins (albumin and TeBG) (25). Plasma glucose concentrations were measured with a Cobas bioanalyzer; SGOT, SGPT, BUN, creatinine and albumin concentrations were measured with an Autoanalyzer (Beckman, Palo Alto, CA).

Using a previously described method for separation of bound from free hormone (25), competitive binding assays were done to exclude displacement by RU 486 of testosterone or cortisol from their plasma binding proteins, an action that might result in spurious changes in hormone concentrations. Increasing concentrations of RU 486 or unlabled hormone were added to samples with known amounts of radioactively labeled hormone and binding globulin. RU 486 did not displace cortisol from CBG or testosterone from TeBG in concentrations ranging from 10^{-10}–10^{-5} M.

Results

All glucocorticoid-sensitive clinical and biochemical parameters were initially abnormal in this patient, and each became normal during treatment with RU 486 despite continued marked hypercortisolism.

The physical stigmata of Cushing's syndrome, including supraclavicular and dorsocervical fat pads and central obesity, regressed considerably by the conclusion of therapy. This change in fat distribution was not associated, however, with a change in total body weight, which varied between 85 and 89 kg both before and during RU 486 treatment. Maximum daily systolic and diastolic blood pressures decreased steadily during treatment with RU 486, from 200/120 mm Hg before therapy, to 140/90 mm Hg at its conclusion (Fig. 1A). The hypokalemic alkalosis resolved, serum potassium ranged from 3.9–4.6 meq/liter, and serum bicarbonate ranged from 25–29 meq/liter following discontinuation of potassium after the sixth week of RU 486 therapy.

Both subjective and objective psychological measures improved during RU 486 therapy. When the daily dose of RU 486 was increased to 15 mg/kg, Ludiomil therapy was stopped (fourth week of therapy). The patient's depression continued to improve, and he reported increasing attention span, libido, and sense of wellbeing. This subjective improvement was corroborated by self-rating questionnaires and psychiatric interviews.

Plasma glucose levels were initially 140 mg/dl in the fasting state (normal, <105 mg/dl) and 268 mg/dl 2 h after ingestion of 100 g glucose (normal, <140 mg/dl; Fig. 1A). The fasting blood sugar level became normal while the patient was taking RU 486 in a dose of 10 mg/kg·day, and the 2 h postoral glucose tolerance test blood sugar level normalized when he was taking 20 mg/kg (Fig. 1A). Serum TSH concentration was initially subnormal (<0.18 μU/ml) and rose progressively to 1.5 μU/ml during treatment (normal, 0.5–4.5 μU/ml; Fig. 1A). CBG-binding capacity increased from 7.4 μg/dl (normal, 12.2–20 μg/dl) to 16.8 μg/dl (Fig. 1B).

Plasma LH levels rose during treatment with RU 486 from 9.4 to 23.2 mIU/ml (normal, 6–26 mIU/ml; Fig. 1B). Similarly, plasma total and free testosterone concentrations and TeBG-binding capacity increased from subnormal to normal levels during therapy with RU 486 (Fig. 1B). The total testosterone concentration was initially 73 ng/dl (normal, 200–1000 ng/dl) and rose to 842 ng/dl when the patient was taking 20 mg/kg·day RU 486. TeBG capacity increased from 0.063 μg/dl (normal, 0.2–1.0 μg/dl) to 1.02 μg/dl at the conclusion of therapy. Free testosterone increased from 3.5 ng/dl (normal, 5–30 ng/dl) to 17.4 ng/dl.

Twenty-four hour urinary nitrogen excretion fell from 22 g/day (normal, 12–20 g/day) before treatment to 5 g/day at its conclusion. No abnormalities in serum creatinine, BUN, SGOT, or SGPT, urinalysis, electrocardiogram, chest radiography, or physical examination were found during or after therapy. The patient experienced no adverse subjective effects.

In contrast to the marked improvement in these glucocorticoid-sensitive parameters, urinary cortisol, plasma cortisol, and ACTH levels remained significantly elevated throughout the treatment with RU 486. G-50 gel chromatography revealed that 85% of ACTH immunoreactivity was in the same fractions as ACTH-(1–39). Before initiation of RU therapy, the mean plasma ACTH concentration was 165 ± 7.6 (±SE) pg/ml (n = 5); during treatment, it was 241 ± 14 pg/ml (n = 14; normal, 8–15 pg/ml). The range of plasma cortisol concentration was 29–49.5 μg/dl (mean ± SE, 43.5 ± 3.3 μg/dl; n = 7) before and 13.8–56.5 μg/dl (mean ± SE, 31.8 ± 2.0 μg/dl; n = 27) during RU 486 administration (normal, 8–18 μg/dl). Mean daily urinary cortisol excretion rates also were elevated, ranging between 514 and 11,592 μg/day (mean ± SE, 4865 ± 1159 μg/24 h; n = 11) before therapy. During therapy, urinary cortisol excretion was similar and ranged between 106 and 8072 μg/day (mean ± SE, 1175 ± 327 μg/24 h; n = 27; normal, 20–95 μg/24 h).

Plasma steroid precursor concentrations during therapy were within the normal range or mildly elevated. Pregnenolone was 124 ng/dl (normal, <250), 17-hydroxypregnenolone was 135 ng/dl (normal, <250), 17-hydroxyprogesterone was 706 ng/dl (normal, <200), and 11-deoxycortisol was 431 ng/dl (normal, <200).

No side-effects occurred during RU 486 treatment. In the 10th week, because limited availability of RU 486

prevented further treatment, the patient underwent a bilateral adrenalectomy 48 h after discontinuation of therapy and during supplemental glucocorticoid therapy. Tissue vascularity was normal at the time of surgery, and his postoperative course and wound healing were satisfactory.

Discussion

The glucocorticoid antagonist RU 486 ameliorated the clinical and biochemical features of hypercortisolism in this patient. Treatment with RU 486 was associated with redistribution of body fat and resolution of severe depression, hyperglycemia, and hypertension, obviating the need for a variety of medications which he previously required. Several hormonal disorders typical of hypercortisolism (suppressed plasma levels of TSH, LH, testosterone, CBG, and TeBG) also reverted to normal during RU 486 therapy (15, 19).

The satisfactory response to RU 486 administration despite persistent marked elevation of serum and urinary cortisol levels is consistent with studies of its mechanism of action *in vitro* and in animals. RU 486 interacts with the glucocorticoid receptor and thereby blocks the effects of cortisol (7). The mild decline in plasma and urinary cortisol during therapy might be due to an additional effect of RU 486 to diminish adrenal steroidogenesis directly via enzyme inhibition or a result of spontaneous fluctuation in the severity of the syndrome. No major block occurred, however, in the enzymes 3β-hydroxysteroid dehydrogenase-Δ^5,Δ^4-isomerase,21-hydroxylase, 17-hydroxylase, or 11-hydroxylase, as suggested from the levels of measured steroid precursors in the patient's plasma.

Although RU 486 was an effective therapy in our patient with Cushing's syndrome due to ectopic ACTH secretion, control may be more difficult to achieve in patients with hypercortisolism of pituitary origin (Cushing's disease). Previous studies in nonhuman primates and normal subjects suggest that the dose of RU 486 necessary to achieve normal glucocorticoid status in Cushing's syndrome will depend on the plasma free cortisol concentration and the presence of cortisol feedback. In nonhuman primates and normal men and women, doses of RU 486 greater than 5 mg/kg cause an increase in both plasma cortisol and ACTH levels, presumably by antagonizing cortisol feedback at the pituitary or hypothalamus (8–12). In patients with Cushing's disease in whom cortisol feedback is present, ACTH levels may increase, perhaps in an exaggerated manner, as is often the case with ACTH responses to CRH (22) or metyrapone (26). Nevertheless, high doses of a glucocorticoid antagonist may overcome the reserve of the pituitary adrenal axis in patients with Cushing's disease and thus alleviate the toxic effects of hypercorticolism on tissues. If this were true, then an antiglucocorticoid could be used for preparation of patients for surgery.

The lack of side-effects or toxicity associated with RU 486 administration in our patient contrasts markedly with the morbidity that characterizes the other medical treatments for hypercortisolism. Although the incidence of side-effects cannot be established until additional patients are studied, the present experience suggests that RU 486 therapy may be tolerated better than other currently available medical treatments of hypercortisolism. Greater tolerance may yield greater efficacy, since the available medical treatments often cannot be given in fully effective doses because of their side-effects.

One potential problem with RU 486 is that overtreatment might cause glucocorticoid insufficiency. Since glucocorticoid insufficiency cannot be assessed through measurement of adrenal steroids during RU 486 therapy, we suggest that patients be given RU 486 in gradually increasing doses in concert with careful evaluation for signs and symptoms of adrenal insufficiency.

Currently, the major drawback of RU 486 is that it is costly to synthesize and not available in quantities sufficient for extensive clinical study. Despite these problems, RU 486 holds promise as a safe, well tolerated, and effective medical therapy for hypercortisolism that merits further clinical evaluation.

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