BRIEF REPORT

Possible Use of Glucocorticoid Receptor Antagonists in the Treatment of Major Depression: Preliminary Results Using RU 486

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The rationale for the use of antiglucocorticoids in the treatment of major depression has been reviewed. Four patients with chronic severe depression who were resistant to conventional therapies were given RU 486 (200 mg/day) for periods up to eight weeks. Substantial levels of RU 486 were achieved within the first few days, and the levels fell gradually over the week after the treatment was discontinued. In three cases, treatment was stopped before the eight weeks were completed: in one case because of the appearance of a rash, in the others because of side-effects, which, in retrospect, were likely unrelated to the drug. The mean scores on the Hamilton Rating Scale for Depression of three patients decreased. Levels of adrenocorticotrophin, dehydroepiandrosterone and cortisol rose during treatment. These preliminary results suggest that glucocorticoid antagonists may be effective in the treatment of major depression and merit further exploration.

Key Words: mifepristone, glucocorticoid receptor, depression, RU 486, steroids, glucocorticoid antagonist

INTRODUCTION

ypercortisolemia is a common feature of major depression (Murphy 1991a). It was recently shown that major depression resistant to conventional therapy responded to inhibitors of steroid biosynthesis. Data on ten patients have been collected (Murphy 1991b; Murphy et al 1991), and those on a further ten patients are similar (Dhar et al 1989). These results support the hypothesis that altered steroid metabolism is a critical factor in the maintenance of major depression, and that the alteration of steroid metabolism, including the suppression of biosynthesis, may lead to a readjustment of the hypothalamic-pituitary-adrenal axis with remission of the depression.

A related approach to decreasing the effects of steroids is to use a steroid antagonist. RU 486 (mifepristone,17β-hydroxy-11β-(4-dimethylaminophenyl)17α-(1-propynyl)estra-4,9—dien-3-one) has been shown to be a powerful antagonist at both the progesterone and glucocorticoid receptors (Bertagna et al 1984; Gagne et al 1985).

RU 486 has rarely been given to humans for more than a few days. One exception is a study by Kettel et al (1991) of six women with endometriosis who were given RU 486 100 mg/day for three months. Serum cortisol levels and adrenocorticotrophin (ACTH) levels increased slightly

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($p < 0.05$), and all women became amenorrheic, while their pelvic pain improved. Also, a case of Cushing's syndrome resulting from ectopic ACTH syndrome has been successfully treated with RU 486 (Nieman et al 1985) for nine weeks. Interestingly, this patient's suicidal depression also resolved.

To the authors' knowledge this is the first open trial of a glucocorticoid receptor antagonist for the treatment of major depression.

MATERIALS AND METHODS

The selection criteria were similar to those used in a previous study (Murphy et al 1991), i.e., the patients were between the ages of 18 and 65 years. A primary hospital diagnosis of major depression was confirmed independently by a second psychiatrist based on the DSM-III-R criteria; the major depression was severe, with an after-washout total score of 20 or greater on the 21-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960). The patients were classified as suffering from drug-resistant depression, defined as a history of failure to respond to two or more antidepressant drugs given in adequate dosage, for at least four weeks. They had no major medical problems or any condition that might interfere with the absorption, metabolism or excretion of drugs. They had to be able to understand the consent form to participate in the study. Women of child-bearing potential were excluded. Apart from hypercortisolemia, none of the patients had any signs suggestive of Cushing's syndrome.

The protocol was approved by the Ethics Committee of the McGill University Department of Psychiatry, and informed, written consent was obtained from each patient. The protocol was also approved by the Health Protection Branch of Health and Welfare Canada.

Cortisol, dehydroepiandrosterone (DHAS, an important secretory product of the adrenal cortex), ACTH, and routine biochemical and hematological studies were conducted before treatment, weekly during treatment and after treatment. A dexamethasone test (1 mg at bedtime with blood samples drawn at 8:00 am and 4:00 pm the next day) was considered normal if both values were below 140 nM/L.

During treatment, independent psychiatric assessments were carried out weekly, usually by two physicians, using the 21-item HRSD; individual assessors are indicated by different symbols in Fig. 1. Where both assessments were performed the same day, the mean is indicated.

All the patients were admitted to the psychiatric department of the Royal Victoria Hospital. Previous psychotropic medications were withdrawn over a period from three days to three weeks, depending on the medication. RU 486 (200 mg each morning) was begun and continued as long as tolerated, up to eight weeks. Chloral hydrate, diazepam or clonazepam was permitted for insomnia, and acetaminophen for headaches.

Steroid levels were determined using standard radioimmunoassays. The normal range for 8:00 am cortisol is 248 to 690 nm/L. ACTH was determined using the Raduioassay Systems Laboratories kit (ICN Biomedicals Inc., Costa Mesa, CA). The levels of RU 486 were determined by Roussel Inc.

Mean hormone levels before and during treatment were calculated for each individual and compared using the Student's t-test.

Brief patient histories

Patient 1

This 56-year-old man had been depressed more or less continuously for the past seven years. He had mood-incongruent delusions and hallucinations. Many different antidepressants and electroconvulsive therapy (ECT) had little or no effect. He was tried on steroid suppression therapy, but on ketoconazole he developed abnormal results on liver function tests, and on aminoglutethimide and metyrapone, he had a transient remission followed by a relapse while still on therapy. He had been continuously in hospital for more than one year. Since there was some evidence of ischemic brain damage, it was felt that further ECT should not be attempted. Over the two months prior to the study, his mean morning cortisol level was 789 ± 78 SE nM/L (n = 8), and his dexamethasone suppression was normal. Although improvement seemed unlikely, there was little else to offer this patient.

He was given RU 486 (200 mg/70 kg = 2.9 mg/kg) for eight weeks and tolerated the drug well. His scores on the HRSD fell slightly (although there were major fluctuations) from an average of 34 before RU 486 therapy to an average of 28 during therapy. This trend continued for two weeks after stopping RU 486, during which time his scores on the HRSD were 21 and 18. It then rose to previous levels. This improvement during treatment was not statistically significant, and it was decided not to continue the medication beyond the planned duration of eight weeks.

Patient 2

A 63-year-old woman had worked as a piano teacher and had given concerts until she found she could no longer cope with the planning required. She was married and had one son and one daughter. Her first episode of major depression had occurred 16 years earlier, at which time she had responded to imipramine. She continued taking imipramine, and occasionally prochlorperazine and chlorprothixene, over the next 15 years. The second episode occurred seven months before this study; she was very agitated, paranoid and had hallucinations. In this episode, she was treated with tricyclic antidepressants, haloperidol, procyclidine, lorazepam, clonazepam and 14 ECT treatments. She improved, but four months later suffered a relapse, despite continuing ECT (discontinued four months before she began taking RU 486) and fluoxetine

(discontinued four weeks before starting RU 486). Her medical history included a parathyroid adenoma, which had been removed five years earlier, and primary hypothyroidism, for which she was receiving adequate thyroxine replacement. She had also complained of recurring right hip pain, which was investigated extensively but for which no cause was found. Her mean pre-treatment 8:00 am cortisol levels were 613 ± 66 nM/L (n = 7) and suppressed normally with dexamethasone.

She was started on RU 486 (2.5 mg/kg) and responded promptly. She was therefore discharged home. However, her chronic hip pain recurred during the second week of therapy, and after six weeks of therapy she complained that although she did not feel depressed, the medication was making her hip pain worse. She decided to stop the treatment, remained at home for two months, then required further hospitalization.

Patient 3

This 58-year-old woman had a strong family history of mental illness (her mother and three siblings). She had three children who were all well. She was hospitalized for depression on seven occasions between the ages of 41 and 56. Over the year preceding this study, she had been hospitalized four more times. She was felt to be suffering from manic-depression with psychotic features. On her most recent admission to hospital, she was felt to have increased suicidal ideation, and auditory hallucinations were frequent. Over the years, she received many different antidepressant medications, as well as haloperidol, procyclidine, clonazepam, carbamazepine and ECT. A course of ECT given at age 54 resulted in marked improvement, and again at age 57 she improved, so that she was put on ECT twice monthly as maintenance therapy. However, since the beneficial effects declined, it was felt that ECT was no longer of benefit. Her medications, including clonazepam, lorazepam, haloperidol and procyclidine, were discontinued four weeks before starting RU 486. Her mean 8:00 am cortisol level (n = 8) was 922 ± 128 nM/L.

She improved sufficiently after nine days of therapy on RU 486 (3.9 mg/kg). (Her score on the HRSD fell from a pre-treatment average of 31 (eight observations) to 15 and 6.) She was therefore sent to a foster care home. However, she developed a generalized erythematous rash and became very agitated because of it, with a mean HRSD score of 28 on day 13 of therapy. The drug was stopped and the rash disappeared rapidly on antihistamine therapy, but she suffered a relapse, returning to her usual state.

Patient 4

A 53-year-old woman with two children experienced her first episode of depression after the delivery of her first child at age 24. Over the next 16 years, she attempted suicide at least ten times. She was divorced at age 40. From age 48, she was severely depressed and did not respond to many different antidepressants. At age 51, she was given an eight-week course of ketoconazole. She improved rapidly, although the increase in the severity of her usual headaches was a considerable problem during therapy. Nevertheless, she completed the eight-week treatment and remained well on no medication for the next nine months, when she became depressed once again. She refused a second course of ketoconazole because of the headaches, and was given fluoxetine and nortriptyline with no improvement in her depression. Her mean pre-treatment 8:00 am cortisol level was 1,008 ± 240 nM/L (n = 4), which suppressed normally on dexamethasone.

Fluoxetine was stopped 12 weeks before the study. She then received nortriptyline until two weeks before starting RU 486.

After three weeks on RU 486 (starting at 4.4 mg/kg), she improved markedly; she was able to move to a new apartment, arrange her financial affairs and buy a new car. However, she complained of side-effects and therefore during part of the time she took the medication only every other day; she stopped taking it entirely on the 26th day. She complained mainly of diarrhea, which she had had frequently during the six preceding months, after a trip to Mexico; however, she could not be convinced that this was unrelated to the drug. By the end of treatment, her score on the HRSD had fallen by 40%. Her improvement was maintained for several weeks, and then she gradually relapsed. The diarrhea continued to recur.

RESULTS

Relatively high levels of RU 486 (2.3 to 2.5 mg/L) were reached within the first few days, and could be detected for up to nine days after stopping the drug. Since only one treatment dose was available, the relative doses varied from 2.5 to 4.4 mg/kg/day. Patient 4, who weighed only 45 kg, took the medication only every other day for much of the treatment period, and this was reflected in her lower levels (0.5 and 0.8 mg/L) at days 14 and 23, respectively.

ACTH levels rose after RU 486 in all four subjects; the increases were significant in two patients ($p = 0.03$ for patient 2 and $p = 0.0083$ for patient 4; for patient 3 only one value was obtained while she was on RU 486, and this was 332% higher than the mean of the five values obtained before treatment. DHAS levels rose in every case; the rise was significant in one (patient 3, $p \leq 0.0001$) and marginally significant in two (patient 1, $p = 0.11$; patient 2, $p = 0.06$).

Mean pre-treatment cortisol levels were above the normal range in three patients (patients 1, 3 and 4), and during RU 486 administration rose higher in three; the increases were significant in two (patient 1, $p \leq 0.0001$; and patient 2, $p = 0.0013$).

The individual HRSD scores for each patient are shown in Fig. 1. The data are insufficient for non-parametric testing. The mean scores during treatment were all lower than those before treatment, the percentage drop in score being 18, 39,

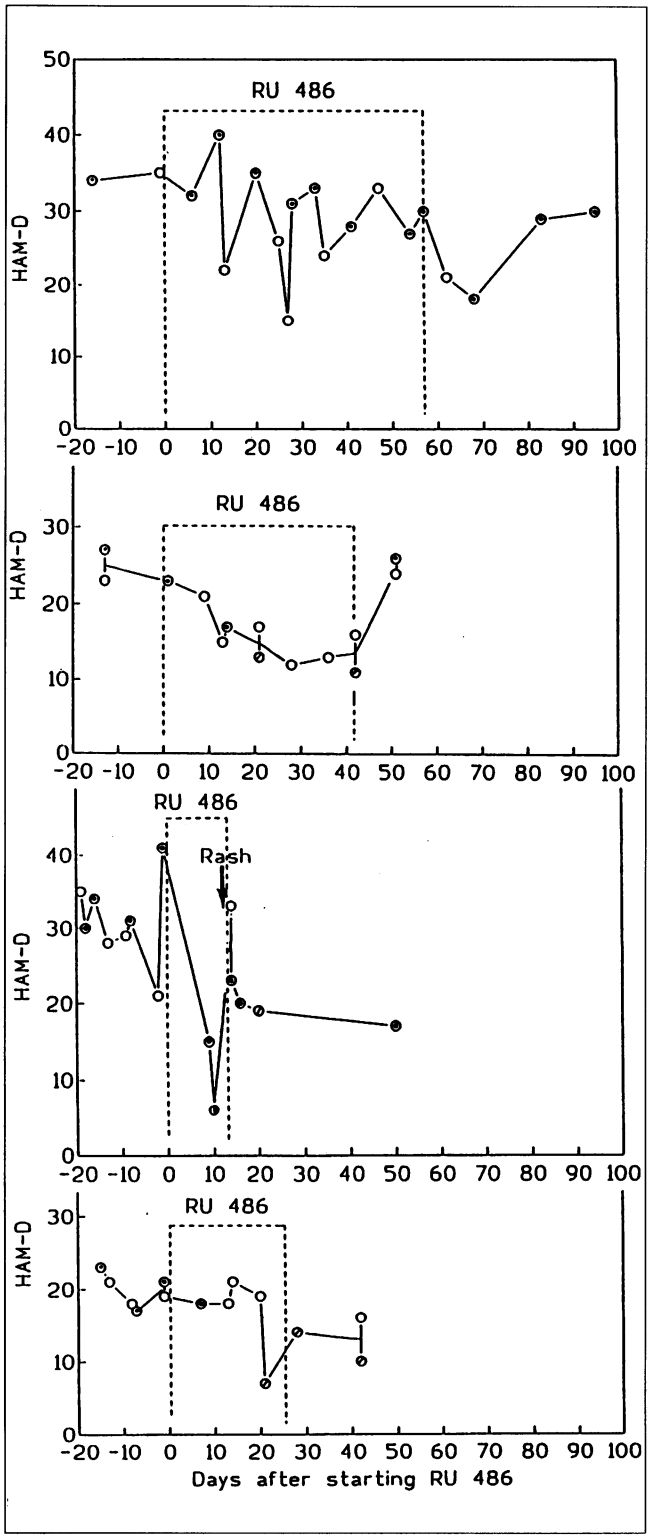

Fig. 1. HRSD ratings for each patient (Patient 1 at the top to Patient 4 at the bottom). Individual physicians who performed the ratings are indicated by different symbols.

66, and 16% for patients 1 through 4, respectively. Using t-tests, which are not strictly applicable here, this difference was significant in two patients (patient 2, $p \leq 0.001$; patient 3, $p \leq 0.0005$). When the data on all four patients were considered, the improvement using t-tests was of marginal significance ($p = 0.08$). When the data on only the three women were included, the difference between the pre-treatment and treatment means was significant ($p \leq 0.04$), while that between treatment and post-treatment was of borderline significance ($p = 0.07$).

DISCUSSION

While the results are not dramatic, they suggest that glucocorticoid antagonists may be of use for treatment-resistant depression. For ethical reasons, only patients who had severe major depression of very long standing and who were extremely resistant to treatment were studied. Unfortunately, only one patient (patient 1) completed the planned course of eight weeks of treatment. His results suggested that he might be responding slowly; however, this could not be tested. Patient 2 did well for six weeks, until she stopped taking the medication because she felt her hip pain had worsened. However, this pain had been a chronic problem for many years for which no abnormality has ever been found. Patient 3 did very well until she developed a rash, at which time the drug was stopped. The rash subsided promptly on antihistamine therapy. Patient 4 also stopped the drug once her depression improved, ostensibly because of recurrent diarrhea; however, it seems unlikely that this problem, which had been present for at least six months before the study and persisted after stopping the treatment, was affected by RU 486. These few studies are not adequate to judge the efficacy of RU 486; however, they are sufficiently encouraging to warrant further investigation.

Peiffer et al (1991) have suggested that antidepressants may act at the glucocorticoid receptor level to increase the number of receptors and thus the sensitivity of the glucocorticoid feedback. This is in agreement with the observations of Gormley et al (1985) and Whalley et al (1986) of lower glucocorticoid receptor site numbers in lymphocytes from depressed patients. Sapolsky et al (1984) have noted that corticosterone receptors are down-regulated in the brain with chronic stress. If such a change occurs in depression, where episodes often appear to be triggered by stress, up-regulation of receptors may be important in inducing remission.

The hormonal results of this study are in accordance with those of other studies (Kettel et al 1991; Nieman et al 1985; Krishnan et al 1992), i.e., a rise in ACTH and cortisol. DHAS levels, which also rose in this study, have not previously been reported.

Unfortunately, the suppliers of RU 486 had decided to cancel the contract for the study at approximately the same time the latter three patients had begun receiving the drug.

However, well-controlled studies using glucocorticoid receptor antagonists are warranted. Unfortunately, no other suitable drugs are currently available.

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