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MONOGRAPH

THE USE OF MIFEPRISTONE IN THE TREATMENT OF CUSHING'S SYNDROME

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SUMMARY

Patients with endogenous hypercortisolism, Cushing's syndrome, have significant morbidity and increased mortality when inadequately treated. When surgical therapy has been unsuccessful other treatment modalities are necessary. Previously available therapies have limited effectiveness or significant toxicity. Mifepristone, a glucocorticoid receptor antagonist, provides a novel approach to the treatment of hypercortisolism. It is rapidly absorbed, highly protein bound and has a long plasma half-life. Since it also serves as a progesterone receptor antagonist, mifepristone has been used in several other medical conditions. A recently published prospective trial of mifepristone therapy for Cushing's syndrome resulted in its recent approval by the U.S. Food and Drug Administration for use in Cushing's syndrome.

Key words: Mifepristone – RU-486 – Cushing's syndrome – Cortisol – Glucocorticoid receptor antagonists

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BACKGROUND

Endogenous hypercortisolism, Cushing's syndrome, is a complex endocrine disorder with multiple etiologies and serious clinical manifestations including obesity, diabetes, hypertension, osteoporosis, gonadal dysfunction, and neuropsychiatric and neurocognitive disorders. If inadequately treated, endogenous hypercortisolism confers a 3.8- to 5.0-fold higher mortality than the general population (1).

Spontaneous Cushing's syndrome may be caused by a pituitary (Cushing's disease) or a nonpituitary (ectopic) adrenocorticotropic hormone (ACTH)-secreting neoplasm or by an adrenal tumor, either benign or malignant. Although previous estimates suggest an annual incidence of less than two cases per million population, more recent studies have shown a greater prevalence in high-risk populations (1). For example, endogenous hypercortisolism occurs in 0.5-1% of patients with hypertension (2, 3), 6-9% of patients with incidental adrenal masses (4, 5), and 11% of individuals with osteoporosis and vertebral fractures (6).

Surgical intervention is the initial mainstay of therapy in almost all patients with Cushing's syndrome; however, many patients do not achieve satisfactory control of their endogenous hypercortisolism following surgery and additional therapies are often needed. Pituitary microsurgery yields a remission rate of 65-90% in patients with tumors < 1 cm but < 65% in patients with tumors > 1 cm. Even those individuals with initial successful surgery have a 5-45% chance of recurrence at 10 years (7-16). External beam radiation therapy may be used as an adjunct in some individuals who fail initial surgery, but even after 3-5 years this is effective in only 50-60% of patients (17-19). Ectopic ACTH-secreting neoplasms may also provide therapeutic challenges since some are radiographically occult at the time of diagnosis of Cushing's syndrome and others may be surgically inoperable. Benign adrenal tumors are usually removed with good surgical outcomes; however, adrenocortical carcinoma is often surgically inoperable and may be associated with severe hypercortisolism. Although bilateral adrenalectomy is effective for the management of patients with ACTH-secreting tumors, the patient has subsequent adrenal insufficiency that requires life-long steroid replacement and is associated with a decreased quality of life (20). Although a minority of patients are not cured with surgical intervention, there are some individuals with Cushing's syndrome in whom medical therapy is needed to control the hypercortisolism.

The medical therapy for patients with Cushing's syndrome has been limited, and until recently no drug had been approved by the U.S. Food and Drug Administration (FDA) for the treatment of Cushing's syndrome. Medications that have been used off-label for the medical control of hypercortisolism include ketoconazole, mitotane, metyrapone and etomidate, which are directed at inhibiting adrenal steroidogenesis. Ketoconazole inhibits several adrenal steroidogenic enzymes and may normalize cortisol secretion in approximately 50-75% of patients (17, 21). However, its effectiveness may be limited by hepatotoxicity and escape from its enzymatic blockade. Mitotane, an agent primarily used in patients with adrenocortical carcinoma, also inhibits steroidogenesis and in higher doses may be adrenolytic. Mitotane has significant toxicities and usually requires several weeks to achieve control of the hypercortisolism. Metyrapone was initially introduced as a diagnostic agent in 1959 but has also been used as a therapeutic agent. It is only available by compassionate use in the United States and there is very little published data confirming its effectiveness in Cushing's syndrome. Etomidate, an inductive anesthetic agent, will rapidly decrease steroidogenesis with subhypnotic doses and may be very effective for the management of gravely ill patients with severe hypercortisolism (22).

In patients with Cushing's disease, pituitary-directed pharmacotherapy has been limited mainly to cabergoline. This long-acting dopamine receptor agonist has been shown to normalize cortisol secretion in 25-40% of patients, but this effect is not durable in the majority of patients (23). Recently, pasireotide, a somatostatin analogue that targets the somatostatin sst_5 receptor subtype, which is expressed in most corticotroph adenomas, has been shown to normalize cortisol secretion in 25% of patients (24).

GLUCOCORTICOID RECEPTOR ANTAGONIST THERAPY FOR CUSHING'S SYNDROME

Steroid receptor antagonists have been used for many conditions. Spironolactone and eplerenone are mineralocorticoid receptor antagonists commonly employed in the management of primary hyperaldosteronism. Additionally, selective estrogen receptor modulators such as tamoxifen are commonly prescribed for patients with estrogen receptor-positive breast cancer.

Mifepristone (11-[4-(dimethylamino)phenyl]-17-hydroxy-17-[1-propynyl]-[11*b*,17*b*]-oestra-4,9-diene-3-one (Fig. 1), a derivative of norethindrone, is a progesterone receptor

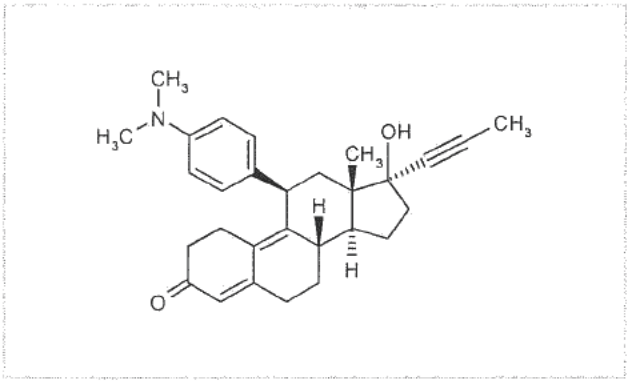


Figure 1. Chemical structure of mifepristone.

antagonist that has glucocorticoid receptor antagonist activity at higher concentration. Mifepristone was discovered in the early 1980s at Roussel-Uclaf and originally named RU-38486 but later shortened to RU-486 (25).

MECHANISM OF ACTION

Mifepristone binds to the human glucocorticoid receptor (previously known as type II glucocorticoid receptor) with an affinity four times higher than that of dexamethasone and about 18 times higher than that of cortisol but has little affinity for the mineralocorticoid receptor (formerly type I glucocorticoid receptor) (26). Mifepristone competes with endogenous cortisol or other synthetic steroids for binding to the glucocorticoid receptor. Once bound to glucocorticoid receptor, the release of associated heat shock proteins and translocation of receptor complexes to the nucleus is prevented (27).

The unique mode of action of mifepristone provides challenges to the clinician monitoring its effectiveness in patients. Glucocorticoid antagonism decreases negative feedback in the hypothalamus and pituitary leading to increased ACTH production and subsequent increased cortisol production in patients with Cushing's disease. Because plasma cortisol levels may rise during mifepri stone therapy, there is no readily available biomarker to determine the impact of treatment.

PHARMACOKINETICS AND METABOLISM

Mifepristone is rapidly absorbed after ingestion and reaches a peak serum concentration within 1-2 hours (28-31). The initial metabolism in human liver microsomes is produced by cytochrome P450 3A4 (CYP3A4). Two of the active metabolites, RU-42633 and RU-42848, are the product of demethylation, while a third active metabolite, RU-42698, results from nondemethylated hydroxylation. RU-42633, RU-42698 and RU-42848 as well as mifepristone itself are all highly bound to α_1-acid glycoprotein (AAG) and albumin. This binding appears to be only slightly concentration-dependent. As serum concentrations of mifepristone rise, saturation of AAG may contribute to the observed nonlinear pharmacokinetics. Serum concentrations of mifepristone rise between doses of 100-800 mg. However, at higher oral doses, the concentrations of the active metabolites continue to increase in a dose-dependent manner and exceed that of mifepristone itself (31, 32). The complex metabolism and the binding of mifepristone, and its metabolites, to plasma proteins make plasma measurement of mifepristone challenging, requiring column and high-pressure liquid chromatography.

Ninety percent of mifepristone and its metabolites are excreted in the feces. Renal excretion into the urine accounts for < 10% of a given dose. The plasma half-life of mifepristone is 24-48 hours, but this underestimates the effective half-life of 54-90 hours that is affected by active metabolites (28, 33).

CLINICAL TRIALS

There is relatively little data on the use of mifepristone in Cushing's syndrome as only one prospective clinical trial has been published on its use in this indication. Until this prospective clinical trial, the treatment of only 37 patients had been reported in the literature. The majority of these patients were reported as a single or small case series. Castinetti et al. summarized the literature and showed that greater than three-quarters of patients treated with mifepristone had improvement in their clinical findings during their first month of therapy (Table I) (34). Importantly, approximately 50% of patients had improved glucose control and reduction in elevated blood pressures. The dosage of mifepristone used and the parameters monitored in each report varies greatly.

Recently, Fleseriu et al. reported the results of the only prospective clinical trial of the use of mifepristone for the treatment of patients with Cushing's syndrome. This was a phase III, 24-week, open-label study in which all 50 patients had documented Cushing's syndrome as well as glucose intolerance and/or hypertension. Patients with all types of Cushing's syndrome (pituitary, ectopic and adrenal) were included. Mifepristone was initiated at 300 mg daily and titrated as necessary to a maximum dose of 1200 mg/day. Improvements in glucose tolerance were seen in 60% of patients with baseline glucose

Table I. *Individual data of patients treated with mifepristone for adrenal carcinoma (patients 1-17), ectopic adrenocorticotropic hormone secretion (patients 18-29), Cushing's disease (patients 30-34) or other causes (patients 35-37).*

Patient No.	Sex/age	Dose mg/day	Previous treatments	Duration months	High BP	Hypokalemia	Adrenal insufficiency	Diabetes
1	F/45	5-22 mg/kg		2				
2	F/32	400		2				
3	F/NA	20-30 mg/kg		4				
4	M/62	400		9			↓	
5	M/43	400-800 mg		0.5				
6	M/63	1000	M	6	↓	↔		↓
7	F/39	400	M	2.5	↔	↑		–
8	F/52	400-600	M	3	↓	↑		–
9	F/52	400-600	M	3	↓	↑		↔
10	F/45	400-2000	M+K	1	–	↑		–
11	F/63	600	M+K	2	↔	–	↑	–
12	M/20	600-1200	M+K	1	↓	↑	↑	↔
13	F/47	400-1200	M+K	2	↔	↑		–
14	F/38	400-600	M+m	3	–	–		–
15	F/44	200-600	M+m	2	–	–		–
16	M/64	200-400	M+m	1.5	–	–		–
17	M/52	600	M+E	0.25	–	↑		↔
18	M/36	5-22 mg/kg		10			↑	
19	M/42	5-22 mg/kg		12				
20	F/63	5-22 mg/kg		4			↑	
21	F/55	5-22 mg/kg		2.5				
22	F/46	800-1600		0.3				
23	M/25	5-20 mg/kg	m+chemotherapy	2.5	↓	↓		↓
24	F/2	75-300	None	2	↓	–		↓
25	F/46	600	Chemotherapy	2	↑	↑		↓
26	F/37	800	Chemotherapy	10	↑	↑		–
27	M/55	400-600	E+m	1	↓	↑		↓
28	F/43	600	K	2	↑	↑		↓
29	F/38	400-800	K	18	↑	↑		–
30	M/45	400-800	K	12	–	–		–
31	M/56	600-1200	K	24	–	–	↑	–
32	F/50	600	–	0.5	–	↔		–
33	F/45	600	–	3	↑	↑		–
34	M/51	400-2000	K	18	↔	↑	↑	–
35	F/38	5-22 mg/kg	–	1.5				
36	F/52	600	K	6	–	↔		↓
37	F/14	400	–	8	–	–		–

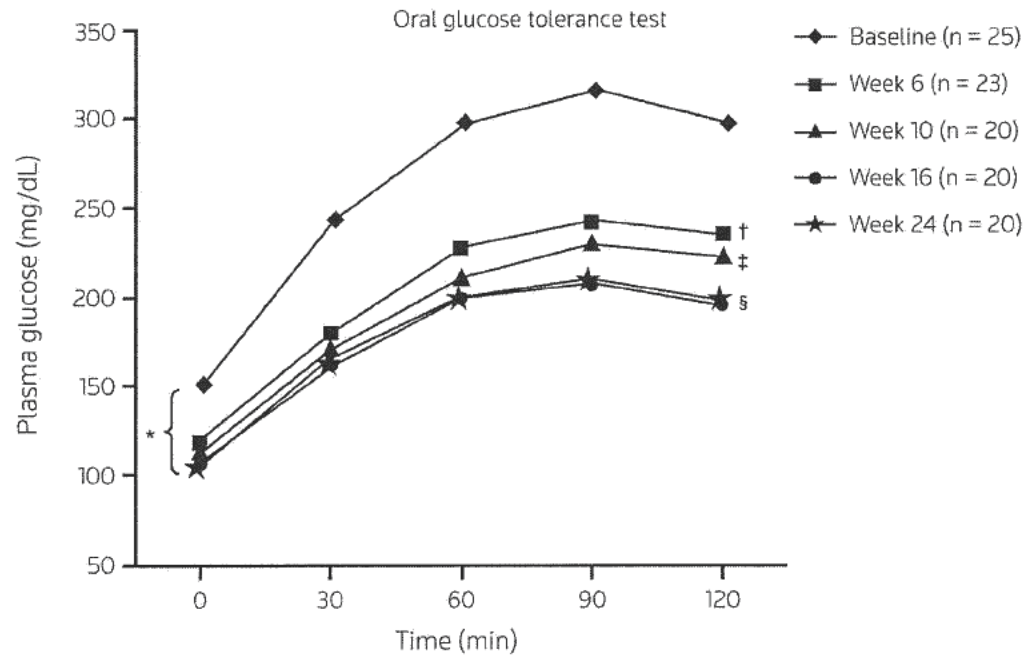
Previous treatments are treatments administered before the start of mifepristone therapy. M, mitotane; K, ketoconazole; m, metyrapone; E, etomidate. High blood pressure (BP), hypokaleima, adrenal insufficiency and diabetes: ↓, alleviation or improvement on mifepristone; ↑, worsening or onset on mifepristone; ↔, unchanged on mifepristone; –, absent before treatment, unchanged on mifepristone; blank space for patients 1-5, not available. (Reproduced with permission from Castinetti, F. et al. *Medical treatment of Cushing's syndrome: glucocorticoid receptor antagonists and mifepristone*. Neuroendocrinology 2010, 92(Suppl. 1): 125-30 (34), S. Karger AG, Basel publishing.)

intolerance. The mean glycated hemoglobin decreased by 1.1% and fasting plasma glucose decreased by 45 mg/dL (Fig. 2). There was also a rapid and dramatic decrease in insulin secretion reflecting improvements in insulin sensitivity with mifepristone. Additionally, 38% of patients with hypertension had improvement in blood pressure. Other findings included weight loss and a significant reduction in waist circumference (Fig. 3). Moreover, a data review board of blinded experts who reviewed the data in these patients concluded that clinical improvement was evident in 87% of treated patients (35).

SAFETY

Mifepristone has been studied in daily dosing in a number of medical conditions; however, the dose in the majority of these conditions (5-100 mg in myoma and endometriosis, and 200-400 mg in meningioma and breast cancer) is much less than that used for cortisol blockade, 300-1200 mg daily (36). The exception is in psychotic depression where mifepristone has been studied for a short duration in doses from 300-1200 mg daily (37). For this reason, the long-term safety of mifepristone in doses appropriate for treatment of Cushing's syndrome is unknown.

The safety of mifepristone use for shorter periods of time or at lower doses has been investigated in several clinical trials for other conditions. For example, use of mifepristone causes decreased menstrual bleeding or amenorrhea in essentially all women. The endometrium in women taking daily mifepristone therapy undergoes characteristic changes with inactive proliferative or cystic changes with a dense stroma (38). Vaginal bleeding is seen in some women and was seen in 14% of women in



Error bars in graph are SE
*$P < 0.03$ FPG baseline to week 24: 149 ± 75 mg/dL vs. 105 ± 38 mg/dL
†$P = 0.004$ vs. baseline
‡$P = 0.003$ vs. baseline
§$P < 0.001$ (week 16 and week 24) vs. baseline

Figure 2. Effects of mifepristone on glucose tolerance in patients with Cushing's syndrome. FPG, fasting plasma glucose. (Reproduced with permission from Fleseriu, M. et al. *Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome*. J Clin Endocrinol Metab 2012, 97(6): 2039-49 (35), Copyright © 2012, The Endocrine Society.)

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