Review Article

A NEW THERAPEUTIC APPROACH IN THE MEDICAL TREATMENT OF CUSHING'S SYNDROME: GLUCOCORTICOID RECEPTOR BLOCKADE WITH MIFEPRISTONE

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ABSTRACT

Objective: Cushing's syndrome (CS) is a serious endocrine disorder caused by prolonged exposure to high cortisol levels. Initial treatment of this condition is dependent upon the cause, but is generally surgical. For patients whose hypercortisolism is not cured by surgery, medical therapy is often required. Drugs that have typically been used for CS medical therapy act by decreasing cortisol levels. Mifepristone is a glucocorticoid receptor antagonist now available for use in patients with CS. Unlike other agents, mifepristone does not decrease cortisol levels, but directly antagonizes its effects. Our objective is to review the pharmacology and clinical use of this novel agent and to discuss detailed guidance on the management of CS patients treated with mifepristone.

Methods: We review the literature regarding mifepristone use in CS and recently published clinical trial data. Detailed information related to clinical assessment of mifepristone use, potential drug interactions, drug initiation and dose titration, and monitoring of drug tolerability are provided.

Results: Clinical trial data have shown that mifepristone improves glycemic control and blood pressure, causes weight loss and a decrease in waist circumference, lessens depression, and improves overall wellbeing. However, adverse effects include adrenal insufficiency, hypokalemia, and endometrial thickening with vaginal bleeding. These findings are supported by the earlier literature case reports.

Conclusion: This article provides a review of the pharmacology and clinical use of mifepristone in Cushing's syndrome, as well as detailed guidance on the management of patients treated with this novel agent. **(Endocr Pract. 2013;19:313-326)**

Abbreviations:
ACC = adrenal cortical carcinoma; **ACTH** = adrenocorticotropin; **AI** = adrenal insufficiency; **$AUC_{glucose}$** = area-under-the-curve for glucose; **CD** = Cushing's disease; **CS** = Cushing's syndrome; **EAS** = ectopic ACTH syndrome; **GR** = glucocorticoid receptor; **TSS** = transsphenoidal surgery

INTRODUCTION

Prolonged exposure to elevated levels of cortisol leads to Cushing's syndrome (CS), a multisystem disorder with a constellation of physical appearance changes, cardiometabolic and neuropsychiatric abnormalities, and

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poor quality of life. The serious morbidity and high mortality of CS are due to excess glucocorticoids, which increase the incidence of type 2 diabetes mellitus, glucose intolerance, insulin resistance, hypertension, central obesity, hyperlipidemia, osteoporosis, hypogonadism, depression, and hypercoagulability (1-7). Several of these abnormalities contribute significantly to the high cardiovascular risk associated with CS, which may persist long after biochemical remission (2,8-10). Therapeutic goals in

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CS include controlling hypercortisolism and addressing the cardiometabolic, physical, and psychological abnormalities that often persist after initial surgical treatment (11) and may have devastating long-lasting consequences (3,12-18).

For adrenocorticotropin (ACTH)-producing pituitary tumors or Cushing's disease (CD), transsphenoidal surgery (TSS) is the treatment of choice, with cure rates of 70 to 90% in experienced centers (11). Recurrence rates after initial surgery are 5 to 25.5% at 5 years and 10 to 20% at 10 years for CD, with recurrences seen as late as 20 years (19-24), necessitating prolonged follow-up. Successful outcomes are less likely for pituitary macroadenomas than for microadenomas (25). A second pituitary surgery is associated with lower rates of remission (50 to 70%) (26-29). Other second-line options include medical treatment, radiation therapy, and bilateral adrenalectomy.

In cases of ectopic ACTH syndrome (EAS), surgery cures <50% of patients (30). Most cases of ACTH-independent CS are caused by benign adrenal tumors, for which adrenalectomy is usually curative. In contrast, adrenal cortical carcinoma (ACC) is often unresectable at diagnosis due to extensive local and metastatic disease.

Currently, medical therapy for CD serves a primarily adjunctive role after unsuccessful TSS and/or while awaiting the effects of radiation therapy (29). This holds true for other forms of CS when surgical resection is unsuccessful or not possible. Medical therapy as first-line treatment is reserved for cases where there is urgent medical need for rapid treatment of hypercortisolemia or in patients with contraindications to surgical intervention. There are 3 mechanisms of action for medical therapy: modulation of ACTH release, inhibition of adrenal steroidogenesis, and glucocorticoid receptor (GR) blockade. Until recently, no medications were approved for use in CS by the U.S. Food and Drug Administration (FDA), leading to off-label use of some drugs. Table 1 summarizes the medical therapies used in patients with CS (31-45).

Mifepristone is a GR antagonist recently approved by the FDA for use in CS patients with associated diabetes or glucose intolerance. This review will focus on GR blockade, which is a new therapeutic approach for CS. The concept of hormone receptor blockade for treating endocrine disorders caused by hormone excess is not new and endocrinologists have used this approach successfully in the treatment of hyperaldosteronism (with spironolactone and eplerenone) and acromegaly (with pegvisomant).

MIFEPRISTONE MECHANISM OF ACTION AND PHARMACOKINETICS

Mifepristone is a substituted steroid that directly blocks the GR and the progesterone receptor (46). Mifepristone's affinity for the GR is >3-fold that of dexamethasone and >10-fold that of cortisol (47,48). Peak plasma concentrations occur 1 to 2 hours after a single dose and 1 to 4 hours after multiple doses (49). Three active metabolites of mifepristone account for approximately 50% of its antiglucocorticoid activity (48). Plasma concentrations of mifepristone and its metabolites increase with dose escalations, although they are less than dose proportional (49). Mifepristone is highly protein-bound, with an average elimination half-life of 85 hours after multiple doses (49). Approximately 2 weeks are required to clear mifepristone from the circulation after dosing cessation. Plasma mifepristone levels increase with food in a dose-related manner (by approximately two-thirds for a 1,200 mg dose with a typical fat content meal [34% fat]) (49). Administration of mifepristone with meals leads to more consistent plasma levels of the drug (49).

The maximum recommended mifepristone dose is 1,200 mg daily, but is 600 mg in patients with severe renal failure (creatinine clearance <30 mL/min) and mild to moderate hepatic impairment.

CLINICAL EFFICACY DATA

The SEISMIC (*S*tudy of the *Effi*cacy and *S*afety of *M*ifepristone *i*n the Treatment of Endogenous *C*ushing's Syndrome) trial was a prospective, 6-month, multicenter, open-label study of the efficacy and safety of mifepristone in 50 CS patients (38). The primary endpoint for patients with CS and diabetes mellitus and/or impaired glucose tolerance (C-DM cohort, n = 29) was the change in area-under-the-curve for glucose ($AUC_{glucose}$) during oral glucose tolerance tests. For patients with a diagnosis of hypertension alone (C-HT cohort, n = 21), a reduction in diastolic blood pressure (DBP) was the primary endpoint.

Sixty percent of C-DM patients were responders, defined as patients who experienced ≥25% decrease in $AUC_{glucose}$ (P <.0001), while 38% of C-HT patients were responders, defined as patients who experienced a mean decrease in DBP of ≥5 mm Hg (P <.05). Seven of the 12 C-DM patients taking insulin at baseline reduced their daily dose by ≥50%. Mean hemoglobin A1c also declined over the course of the study, from 7.43% at baseline to 6.29% at study conclusion (P <.001). Global clinical improvement determined by an independent Data Review Board was achieved in 87% of patients (P <.0001). Body weight decreased by 5.7% (P <.001), and >50% of participants lost ≥5% of their baseline weight; mean waist circumference decreased by 6.8 cm in females and 8.4 cm in males (P <.001 for both groups).

Adverse events related to the pharmacology of mifepristone included low potassium levels (hypokalemia), adrenal insufficiency, and endometrial thickening. Nausea and fatigue were common adverse events (Table 2).

These positive results are consistent with earlier published case reports and retrospective studies involving mifepristone (Table 3) (46,50-64). A majority of patients

Table 1
Drugs Used for the Medical Treatment of Cushing's Syndrome

Drug	Doses	Efficacy/benefits	Adverse effects/limitations
Inhibitors of ACTH secretion			
Octreotide		50% response in ectopic ACTH, short-term responses (45)	Poorly effective for Cushing's disease (43)
Pasireotide	600-900 mg SQ BID	Phase 3 results: Median UFC change from baseline was –47.9%; UFC normalization in 20.4%; higher rate of UFC normalization with lower baseline UFC; Early identification of nonresponders: >90% of patients uncontrolled at months 1 and 2 remain uncontrolled at month 6 (32,35)	Adverse effects similar to other somatostatin analogs, with the exception of hyperglycemia and diabetes mellitus
Cabergoline	1.5-7 mg/week PO	Initial remission in up to 50%; variable responses (39,41)	Nausea, dizziness, hypotension, possible cardiac valvulopathy at high doses; escape from effect on cortisol
Inhibitors of adrenal steroidogenesis			
Ketoconazole	400-1200 mg/day PO	50% of patients with controlled cortisol (33,34)	Hepatotoxicity, liver failure (rare), gastrointestinal complaints, hypogonadism, gynecomastia in men
Metyrapone	500-6000 mg/day PO	Up to 80% of patients with controlled cortisol (44)	Escape from effect on cortisol, increased ACTH, hirsutism in women, hypokalemia, hypocortisolism; available upon request
Mitotane	Up to 6000 mg/day PO	Up to 90% short-term remission in ectopic ACTH (40); up to 70% remission in Cushing's disease (31,36,40,42)	Slow onset of action; poor tolerability due to neurologic, gastrointestinal, and hepatic effects; can reduce aldosterone levels and require mineralocorticoid replacement; teratogenic; reserved mainly for ACC in the United States
Etomidate	0.03-0.3 mg/kg/hr IV	Rapid onset; useful for acute control of severe hypercortisolism (37)	Sedation, parenteral
Glucocorticoid receptor blocker			
Mifepristone	300-1200 mg/day PO	Clinical responses in up to 87% of patients; improved glucose metabolism, insulin sensitivity, weight loss (38)	Hypokalemia; vaginal bleeding; inability to use cortisol levels for monitoring; nausea/ fatigue common; decline in HDL-cholesterol and increase in TSH, which are reversible upon drug discontinuation

Abbreviations: ACC = adrenal cortical carcinoma; ACTH = adrenocorticotropin hormone; BID = twice a day; HDL = high-density lipoprotein; IV = intravenously; PO = orally; SQ = subcutaneous; TSH = thyroid-stimulating hormone; UFC = urinary free cortisol.

described in these publications (16 with EAS and 17 with ACC) showed resolution or significant improvement in somatic features of CS. Improvements related to diabetes, including reductions in antidiabetic medication doses and rapid resolution of psychiatric symptoms, were also frequent. Other beneficial effects included normalization of blood pressure and reversal of heart failure. Hypokalemia was noted in 15 patients (50,53,54,56). Adrenal insufficiency (AI) was reported in 4 patients (55,56,60), and suggestive symptoms and signs (e.g., nausea, lethargy, vomiting) led the authors to consider AI in 8 additional patients (54,55,57,58). Because cortisol levels cannot be used to diagnose AI during mifepristone treatment (see below), and because formal safety reporting was not employed, the true rate of AI in the patients described in these reports is uncertain.

Table 2
Adverse Events Occurring in ≥10% of Patients With Cushing's Syndrome Taking Mifepristone

Body system/adverse event	Percent of patients reporting event (N = 50)
Gastrointestinal disorders	
Nausea	48
Vomiting	26
Dry mouth	18
Diarrhea	12
Constipation	10
General disorders and administration/site conditions	
Fatigue	48
Edema peripheral	26
Pain	14
Nervous system disorders	
Headache	44
Dizziness	22
Somnolence	10
Musculoskeletal and connective tissue disorders	
Arthralgia	30
Back pain	16
Myalgia	14
Pain in extremity	12
Investigations	
Blood potassium decreased	34
Thyroid function test abnormal	18
Infections and infestations	
Sinusitis	14
Nasopharyngitis	12
Metabolism and nutrition disorders	
Decreased appetite	20
Anorexia	10
Vascular disorders	
Hypertension	24
Reproductive system and breast disorders	
Endometrial hypertrophy	38[a]
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	16
Psychiatric disorders	
Anxiety	10

[a]The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound.

Table 3
Summary of Case Reports of Mifepristone Use in Cushing's Syndrome

Reference	N	Clinical findings	Safety observations
Basina et al 2012 (50)	1	Cushing's disease Cushing's symptoms markedly improved; weight loss improved energy reduced striae	Hypertension Hypokalemia
Beaufrère et al 1987 (51)	1	ACTH-dependent Cushing's: unknown etiology Weight loss Reduction of blood pressure and glucose to normal levels Plasma and urinary cortisol and ACTH levels decreased	No side effects noted
Bilgin et al 2007 (52)	1	Ectopic ACTH Normalization of ACTH and cortisol levels and metabolic disorders Psychosis resolved Mifepristone coadministered with etomidate	No adverse events reported Progression of metastatic lung cancer quickly led to death
Cassier et al 2008 (53)	2	Case 1: Ectopic ACTH Improvement of diabetes mellitus and facial and truncal swelling within 3 months Symptoms returned after 10 months of therapy and, except for glycemic control, did not respond to increased mifepristone doses Case 2: Ectopic ACTH Facial swelling, muscular weakness, hypertrichosis, and skin hematomas improved within 3 months Fasting blood glucose and HbA1c normalized Hypokalemia and hypertension continued	Case 1: Ectopic ACTH No side effects on liver, kidney, or thyroid Required spironolactone and large amounts of supplemental potassium Case 2: Ectopic ACTH Progression of tumor with persistent hypertension and continuing hypokalemia Required spironolactone and large amounts of supplemental potassium
Castinetti et al 2009 (54)	4	Cushing's disease Rapid improvement of clinical signs observed in 3 of 4 patients Psychiatric symptoms improved in 1 of 1 patients within the first week Increases in ACTH and cortisol in all patients	Cushing's disease Signs of adrenal insufficiency in 1 patient High blood pressure and severe hypokalemia in 1 patient
	3	Ectopic ACTH Improvement of clinical signs observed in 3 of 3 patients Psychiatric symptoms improved in 1 patient with these symptoms within the first week Insulin doses decreased or switched to oral antidiabetic drugs with good glucose control in 2 of 2 patients	Ectopic ACTH Worsening hypokalemia in 3 patients Worsening hypertension in 2 patients
	12	Adrenal carcinoma Rapid improvement of clinical signs observed in 8 of 12 patients within the first month Blood pressure decreased in 4 of 7 hypertensive patients Psychiatric symptoms improved in 1 of 2 patients within the first week Switch from insulin to oral anti diabetic drugs in 1 of 4 patients with diabetes	Adrenal carcinoma Signs of adrenal insufficiency in 2 patients 7/12 patients developed new or worsened hypokalemia, which was severe in 2 patients, required spironolactone in 3 patients, and resulted in discontinuation of mifepristone in 1 patient; potassium supplementation required
	1	Adrenal hyperplasia Improvement of clinical signs during first 3 months Metformin therapy stopped after 1 month; HbA1c levels improved after 6 months	Adrenal hyperplasia Hypokalemia unchanged

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