Mifepristone for Management of Cushing's Syndrome

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Cushing's syndrome is a debilitating endocrine disorder caused by elevated circulating glucocorticoid levels. Although uncommon, Cushing's syndrome is associated with significant morbidity necessitating rapid reversal of hypercortisolemia. Primary therapy for most patients with Cushing's syndrome is surgical, but many patients will require additional treatments with radiation or drugs. Although several options for drug therapy exist, few are readily available and all have dose-limiting adverse effects. Mifepristone (RU 486), a first-in-class glucocorticoid receptor antagonist, was approved by the United States Food and Drug Administration in 2012 for use in Cushing's syndrome to control hyperglycemia in patients who are not surgical candidates or have not achieved remission from surgery. The drug is approved for oral once-daily administration. In its pivotal trial, 60% of patients responded to mifepristone with significant improvements in glycemic control and 38% had a reduction in diastolic blood pressure. The most common adverse events were nausea, fatigue, headache, endometrial hyperplasia, and hypokalemia. Adrenal insufficiency occurred in fewer than 5% of patients. The recommended starting dosage of mifepristone is 300 mg/day. The dosage may be increased every 2–4 weeks up to a maximum of 1200 mg/day, although it should not exceed 20 mg/kg/day. Significant drug–drug interactions exist due to mifepristone's effects on a number of cytochrome P450 enzymes. Despite its limitations, mifepristone is a welcome addition and an appropriate alternative to the available drug therapy for Cushing's syndrome.

Key Words: mifepristone, glucocorticoid receptor antagonist, Cushing's syndrome, Cushing's disease, RU486.

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Cushing's syndrome is a rare but debilitating endocrine disorder caused by excess circulating glucocorticoids. The excess glucocorticoids result from increased glucocorticoid production in the adrenal gland secondary to adrenal stimulation or a primary adrenal tumor. For most forms of Cushing's syndrome, the initial treatment is surgical. However, a substantial proportion of patients will not be cured by surgery. Second-line therapy can include additional surgery, radiation, or pharmacologic agents. Previously available drugs have primarily been inhibitors of adrenal steroid synthesis, and the use of these agents has been limited by availability and tolerability. Mifepristone, a first-in-class glucocorticoid receptor antagonist, was approved by the United States Food and Drug Administration (FDA) in 2012 for use in patients with hyperglycemia secondary to Cushing's syndrome. With approval of this new agent, prac-

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pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, indications for use, and limitations.

Cortisol: Normal Physiology

Secretion of cortisol is maintained by a classic endocrine feedback system. Cortisol production occurs in the zona fasciculata cells of the adrenal cortex. These cells are stimulated by adrenocorticotrophic hormone (ACTH), which is secreted by corticotroph cells in the anterior pituitary gland. ACTH production is stimulated by corticotrophin-releasing hormone (CRH) produced in the paraventricular nucleus of the hypothalamus. Circulating cortisol then provides negative feedback to inhibit production of CRH and ACTH. Thus, cortisol dynamics depend on normal hypothalamic, pituitary, and adrenal function—the hypothalamic-pituitary-adrenal axis (Figure 1). Normal cortisol levels follow a circadian rhythm with a peak in the early morning (7:00–9:00 A.M.) and a nadir at 11:00 P.M. CRH production is further regulated by physiologic and emotional stress.[1]

Cortisol is necessary to sustain life. It plays a role in multiple essential functions including carbohydrate, protein, and lipid metabolism and vascular tone and blood pressure maintenance. It is also involved in the immune system and responses to stress. Glucocorticoids exert their actions mainly through binding at the glucocorticoid receptor, a member of the thyroid and steroid hormone receptor superfamily of nuclear transcription factors. As would be expected, the glucocorticoid receptor is expressed widely in peripheral tissues and brain regions. Many glucocorticoids, including cortisol, also have affinity for the mineralocorticoid receptor. However, under normal circumstances, the renal mineralocorticoid receptor is "protected" from cortisol binding by the local activity of type 2 11β-hydroxysteroid dehydrogenase (11β-HSD), which converts cortisol to cortisone and does not bind to the mineralocorticoid receptor. Under physiologic circumstances, aldosterone is the primary activator of the mineralocorticoid receptor; its activation promotes sodium retention (and therefore maintenance of blood pressure) and potassium excretion.[1, 2]

Deficiency of cortisol results in the signs and symptoms of adrenal insufficiency, which can vary in severity from fatigue and anorexia to hypotension and hypoglycemia to shock and death. Cortisol excess results in Cushing's syndrome.

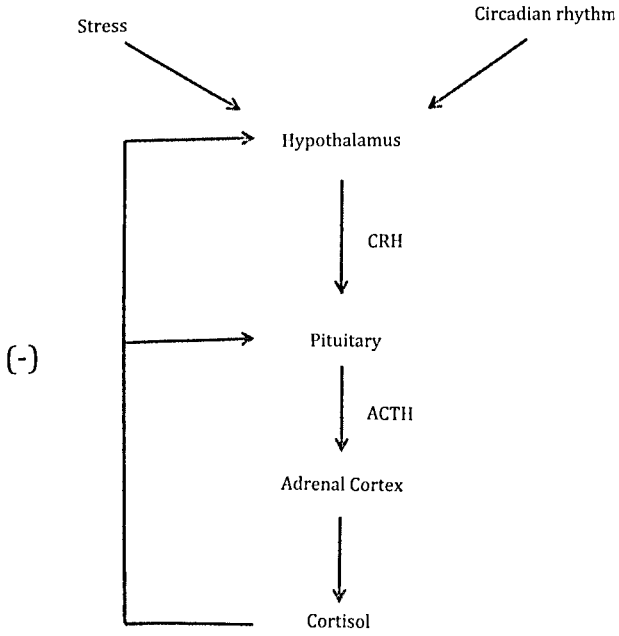

Figure 1. Normal regulation of the hypothalamic-pituitary-adrenocortical axis.[1, 2] ACTH = andrenocorticotrophic

Cushing's Syndrome

Cushing's syndrome is the result of excess circulating glucocorticoids. Exogenous, or iatrogenic, Cushing's syndrome is common and typically results from the use of supraphysiologic doses of glucocorticoids to treat pulmonary, rheumatologic, hematologic, or other disorders. Endogenous Cushing's syndrome is rare and results from inappropriate activation of either the pituitary gland or adrenal glands, leading to increased circulating cortisol levels. The majority of cases are caused by an ACTH-secreting tumor of the pituitary gland (i.e., Cushing's disease). Cushing's syndrome may also result from ectopic secretion of ACTH by neoplasms such as small cell lung cancer and carcinoid tumors; rarely, a tumor may secrete CRH. Cushing's syndrome can also result from benign, malignant, or hyperplastic diseases of the adrenal glands that secrete cortisol in the absence of ACTH stimulation.[3–5]

The excess cortisol seen in Cushing's syndrome results in hypertension, hyperglycemia, obesity, and a myriad of other problems (Table 1).[5] These complications lead to significant morbidity related to illness and twice the mortality rate in patients with Cushing's syndrome compared to the general population.[6]

Table 1. Signs and Symptoms of Cushing's Syndrome[5]

Symptoms	Signs	Other Conditions
Depression	Obesity (especially central obesity)	Hypokalemia
Fatigue	Facial plethora	Hypertension
Weight gain	Moon facies	Diabetes mellitus
Irregular menses	Easy bruising	Osteoporosis
Back pain	Striae (especially wide violaceous striae)	Renal calculi
Insomnia	Proximal myopathy	
Muscle weakness	Dorsocervical fat pad	
Irritability	Supraclavicular fat pads	
	Edema	
	Acne	
	Thin skin	
	Hirsutism	
	Female balding	

important predictors of death.[6] Hypertension occurs in 80% of patients with Cushing's syndrome and is thought to be caused by the effect of cortisol on both the glucocorticoid receptor and the mineralocorticoid receptor.[4] The excess cortisol overwhelms the ability of type 2 11β-HSD to convert it to cortisone, and thus cortisol has access to and activates the mineralocorticoid receptor. Impaired glucose tolerance or type 2 diabetes also occurs in 80% of patients as a result of increased insulin resistance and impaired insulin secretion.[6] Glucocorticoids increase insulin resistance through actions on liver, skeletal muscle, and adipose tissue. The net result of increased liver gluconeogenesis and decreased glucose uptake in skeletal muscle and adipose tissue is hyperglycemia.[6] Impaired insulin secretion also occurs as a result of glucocorticoids binding to pancreatic β cells, resulting in impaired β-cell function.[6] This combined effect causes hyperglycemia that can be very difficult to treat, often requiring escalating doses of insulin for appropriate management.

Diagnosis of Cushing's Syndrome

Because of the complexity of the screening and diagnostic algorithms for Cushing's syndrome, referral to an endocrinologist is appropriate when the disorder is suspected. Accurate diagnosis of Cushing's syndrome is critical to avoid unnecessary testing, procedures, and expenditures.[5, 7]

Before considering biochemical testing for endogenous Cushing's syndrome, it is important [illegible] causing iatrogenic Cushing's syndrome. Initial testing can include measurement of 24-hour urine free cortisol, late-night salivary cortisol collected at 11:00 P.M. or 12:00 A.M., or early morning cortisol after dexamethasone 1 mg the previous evening at 11:00 P.M. (overnight dexamethasone 1-mg suppression test). When an abnormal result is obtained, a physiologic cause of hypercortisolemia, such as depression or other psychiatric illness, alcohol abuse, physical stress, malnutrition, or pregnancy, should be excluded.[5, 8, 9]

After establishment of the diagnosis of Cushing's syndrome, the endocrinologist must determine the source of the hypercortisolemia. A low or undetectable ACTH level should raise the suspicion for an ACTH-independent source, and imaging of the adrenal glands should be performed. An elevated or nonsuppressed ("inappropriately normal") ACTH level reflects an ACTH-dependent source of hypercortisolemia. A combination of noninvasive biochemical testing (high-dose dexamethasone testing or CRH stimulation), pituitary magnetic resonance imaging, and, often, inferior petrosal sinus sampling for ACTH may be necessary to determine if the source is an ACTH-secreting pituitary adenoma or a nonpituitary tumor with ectopic ACTH production.[5, 10]

Treatment Options for Cushing's Syndrome

Treatment of Cushing's syndrome is dependent on the identified source of the disorder. Patients with cortisol-secreting adrenal adenomas are usually cured with unilateral adrenalectomy, whereas patients with adrenocortical carcinoma often have persistent or recurrent disease after surgery due to local invasion or metastases. In patients with the ectopic ACTH syndrome, initial treatment is directed at the underlying neoplasm. Medical therapies are often needed in patients with persistent hypercortisolemia.

In patients with Cushing's disease (ACTH-secreting pituitary adenomas), who make up the majority of patients with Cushing's syndrome, the primary treatment modality is transsphenoidal surgery, which results in remission rates of 50–80%.[3, 11–14] If there is failure to attain remission after initial surgery or if the disease recurs later, second-line interventions include repeat surgery, radiotherapy, bilateral adrenalectomy, or pharmacologic therapy.[3, 13, 15]

Medical therapy for hypercortisolemia is provided to patients who are unable to undergo [illegible]

who have failed to achieve remission with other treatment modalities, as a bridge to radiotherapy or surgery, or as a palliative option. A number of potential targets exist for medical therapy, including inhibition of steroidogenesis, inhibition of ACTH secretion, and steroid receptor antagonism. The most commonly used agents are steroidogenesis inhibitors such as ketoconazole, metyrapone, and mitotane. Other agents in this class include aminoglutethimide and etomidate (Table 2).[3, 13, 16–20]

Steroidogenesis inhibitors are considered adrenal-directed medical therapy because they control cortisol production by directly decreasing adrenal hormone production. Ketoconazole is the most commonly used steroidogenesis inhibitor because of its availability and relatively rapid onset of action. Ketoconazole was developed as an antifungal drug. It inhibits cortisol synthesis by preventing cholesterol side chain cleavage, inhibiting cytochrome P450 enzyme 17,20-lyase, and inhibiting 11β-hydroxylase, the enzyme involved in the final step of cortisol synthesis. Its major limiting adverse effect is elevated liver enzyme levels, which occur in up to 10% of patients. It can also cause hypogonadism in men because of inhibition of testosterone synthesis.[16, 19–21]

Metyrapone blocks the production of cortisol through inhibition of 11β-hydroxylase. This effectively reduces hypercortisolemia, but because metyrapone is specific for a single enzyme late in the steroid biosynthesis pathway, there is often a dramatic rise in steroids formed proximal to 11β-hydroxylase, particularly 11-deoxycortisol, a mineralocorticoid that causes the frequent adverse effects of hypokalemia, edema, and hypertension. An increase in adrenal androgens can cause hirsutism in women. In an effort to limit the accumulation of precursor steroids, metyrapone is often used in combination with other medical therapies such as ketoconazole. It is currently available in the United States directly from the manufacturer.[16, 19, 20, 22]

Mitotane is used most often for the management of adrenocortical carcinoma. It works through the inhibition of multiple enzymes[19] and, unlike other agents, is directly cytotoxic to adrenocortical cells. Undesirable features of mitotane are its delayed onset of action and dose-limiting gastrointestinal effects. Serious neurologic effects, including ataxia, vertigo, and confusion, also occur at higher doses. These

able 2. Drug Therapy for the Treatment of Cushing's Syndrome[3, 13, 16-20]

rug	Dose Range	Mechanism of Action/Site of Action	Adverse Reactions	Comments
etoconazole	200 mg b.i.d.–400 mg t.i.d.	Inhibition of cortisol synthesis: 11β-hydroxlase, 17-hydroxylase, and C17, 20 lyse	Hepatotoxicity, hypogonadism	Drug interactions due to inhibition of CYP3A
letyrapone	250–1500 mg q.i.d.	Inhibition of cortisol synthesis: 11β-hydroxylase	Hypertension, edema, hypokalemia, hirsutism	Limited availability, often combined with another agent
litotane	500–3000 mg t.i.d.	Inhibition of cortisol synthesis: 11β-hydroxylase and cholesterol side chains	Gastrointestinal effects, ataxia, confusion	Slow onset
minoglutethimide	250 mg b.i.d.–2000 mg q.i.d.	Inhibition of cortisol synthesis and side chain cleavage: 11β-hydroxylase and 18 hydroxylase	Rash, fever, dizziness, depression	Limited availability and efficacy
tomidate	0.1–0.3 mg/kg/hr	Inhibition of cortisol synthesis: 11b-hydroxylase, 17 hydroxylase, and C17, 20 lyse	Sedation	Intravenous administration only
romocriptine	2.5–40 mg/day	Dopamine agonist	Nausea, hypotension	Limited efficacy
abergoline	1–2 mg/wk	Dopamine agonist	Nausea, hypotension	Limited efficacy
asireotide	600–900 μg b.i.d.	Somatostatin analog, somatostatin type 5 receptors	Hyperglycemia	In phase III trials
lifepristone	300–1200 mg/day	Glucocorticoid receptor antagonism	Hypokalemia, adrenal insufficiency, endometrial hyperplasia, nausea	Expensive, difficult to monitor therapy

YP = cytochrome P450.

and it must often be used in combination with another drug to attain more rapid control of hypercortisolemia.[3, 19, 23]

Aminoglutethimide and etomidate are steroidogenesis inhibitors that are used infrequently due to their limitations. Aminoglutethimide, which works by inhibiting the conversion of cholesterol to pregnenolone, is neither particularly effective as monotherapy nor readily available in the United States.[16, 19] Etomidate, an intravenous agent used for anesthesia induction, inhibits cholesterol side chain cleavage and 11β-hydroxylase. It has been used in emergent settings for the rapid control of hypercortisolemia but is not practical for routine use due to its sedative effects.[16, 19, 24]

Drugs that suppress ACTH secretion have been investigated for use in the management of Cushing's disease. Among these are dopamine agonists and somatostatin analogs. Dopamine agonists are potentially attractive agents for the treatment of Cushing's syndrome because of the potential for decreased prevalence of glucose intolerance and diabetes,[6, 13, 16, 25] but results have been variable and few patients with Cushing's syndrome experienced sustained improvement after receiving dopamine agonist therapy.[13, 19, 20] Bromocriptine causes an acute decrease in ACTH, although this effect is not sustained over time with repeated dosing.

Octreotide, a somatostatin analog that predominantly acts on type 2 somatostatin receptors, is largely ineffective in lowering ACTH levels.[13, 16] A newer multiligand somatostatin analog, pasireotide (SOM230), has been demonstrated to inhibit ACTH release in human corticotroph cells through interaction with type 5 somatostatin receptors.[6, 16, 26] Its use has resulted in reduced urine free cortisol levels and improved features of Cushing's syndrome in phase II and III studies, but it appears to have the undesirable effect of hyperglycemia,[17, 27] possibly caused by direct inhibition of insulin and incretin hormone secretion.

Mifepristone

Mifepristone (RU486), a derivative of the synthetic progestin norethindrone, was discovered in the 1980s at the French pharmaceutical company Roussel-Uclaf as part of a special research project to develop antiglucocorticoid compounds.[28] Its antiprogestin effects were quickly recognized, and it was developed as an abortifacient because of its effectiveness in pregnancy termination, particularly when combined with a prostaglandin. Other investigated uses that take advantage of its antiprogesterone activity include the treatment of meningioma and breast cancer. Unfortunately, research on mifepristone has been hindered by the controversy surrounding its use as an abortion pill.[28]

Mifepristone is a selective antagonist of the progesterone receptor at lower doses and blocks the glucocorticoid receptor at higher doses.[18] Mifepristone occupies glucocorticoid receptors with an affinity that is 4-fold higher than that of dexamethasone and 18-fold higher than that of cortisol.[28] After binding, it inhibits transcriptional activation of the glucocorticoid receptor, thereby decreasing the physiologic effects of hypercortisolemia. It blocks both central (negative feedback on CRH and ACTH) and peripheral actions of cortisol.[28] Antagonism of negative feedback of cortisol results in increased circulating ACTH and cortisol levels.[28, 29] It has little affinity for the mineralocorticoid receptor and estrogen receptors but is a weak antiandrogen. Mifepristone is also a weak glucocorticoid agonist, roughly 1/250th of that of cortisol, although this weak effect is unlikely to prevent adrenal insufficiency.[28–30]

Pharmacokinetics and Pharmacodynamics

Mifepristone is readily absorbed after oral ingestion with a bioavailability exceeding 30%.[31] Time to peak plasma concentrations after oral administration of a single dose is 1–2 hours, increasing to 1–4 hours with repeated doses. Food increases the plasma concentrations of mifepristone. Mifepristone has three active metabolites, all of which have high affinity and antagonism for the glucocorticoid receptor (~50% of that of mifepristone). Cytochrome P450 (CYP) 3A is involved in the metabolism of mifepristone. Two of the known active metabolites are a result of demethylation, whereas the third is a result of hydroxylation. Mean plasma concentration of these metabolites peaks between 2 and 8 hours after multiple doses of the drug and eventually exceeds that of mifepristone.[18] Therefore, drug interactions affecting enzyme metabolism may affect the degree of antagonism of the glucocorticoid receptor. Time to steady state with repeated daily dosing is 2 weeks. Mifepristone has a very long elimination half-life of 85 hours after repeated dosing.[18]

Significant drug–drug interactions exist

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