Medical management of Cushing disease

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Although transsphenoidal excision of the adrenocorticotropic hormone (ACTH)–producing neoplasm is often treatment of choice in patients with Cushing disease, medical management is itself a useful preoperative temporizing measure, an option for long-term management in nonsurgical candidates, and an option for patients in whom surgery and/or radiotherapy have failed. Three pathophysiologically based approaches exist in the research literature—neuro-modulation to limit ACTH levels, adrenal enzyme inhibition, and glucocorticoid receptor antagonism. Unfortunately, the neuromodulatory approach involving agents such as bromocriptine, cyproheptadine, octreotide, and valproate has yielded only suboptimal results. Glucocorticoid receptor antagonism remains in its infancy but may overall be limited by side effects and a resultant increase in ACTH and cortisol levels. Adrenal enzyme inhibitors, however, offer substantial future promise in the management of Cushing disease but are limited by the potential need to use them indefinitely and by dose-tolerance effects.

Although etomidate is a potential intravenous alternative for acute cortisol level control, ketoconazole has shown efficacy in the long-term treatment of patients with the disease. Metyrapone and/or aminoglutethimide can be added to ketoconazole if additional control is needed. If success is still not achieved, the potent adrenolytic agent often used for adrenocortical carcinomas, mitotane, is another alternative. (DOI: 10.3171/FOC-07/09/E10)

KEY WORDS • aminoglutethimide • Cushing disease • etomidate • ketoconazole • metyrapone • mitotane

T RANSSPHENOIDAL excision of tumors producing ACTH is the optimum treatment for Cushing disease, with cure rates typically approaching 80%. At times, subtotal hypophysectomy (85–90%) is used in patients without clearly identifiable adenomas. Nonsurgical approaches are advocated in patients with incompletely resected pituitary macroadenomas or carcinomas, patients with adenomas and multiple medical issues precluding surgery, and patients with adenomas wishing to preserve fertility. Whereas medical therapy has been used preoperatively, it can also be employed alone or as an adjunct to radiotherapy in such nonsurgical candidates and in those in whom surgical and/or radiation treatment has failed. Unfortunately, such an approach generally requires life-long use of the medications unless adjunctive radiotherapy has been given. Three pharmacological approaches have been attempted—one involving neuromodulatory compounds aimed at limiting pituitary ACTH secretion, another involving glucocorticoid receptor antagonists such as mifepristone, and another involving adrenal enzyme inhibitors.

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Attempts with neuromodulatory compounds such as bromocriptine, cyproheptadine, octreotide, and valproate have yielded only marginal results. Among these agents, bromocriptine has had the highest documented response rate—slightly less than 25%,16 potentially attributable to the fact that some ACTH-secreting neoplasms express D2 receptors. Additionally, despite promising results in animals, rosiglitazone did not prove useful in the management of Cushing disease in humans.9

High-dose mifepristone, a well-known abortifacient (known as RU486) and competitive antagonist to glucocorticoids, remains in its infancy in its utility in Cushing disease. Given this agent’s mechanism of action, efficacy must essentially be judged by clinical response rather than

Abbreviation used in this paper: ACTH = adrenocorticotropic hormone.
serum levels of ACTH or cortisol; in fact, resultant elevated levels of ACTH may ultimately limit its utility given the inability to distinguish whether such an elevation is due to the medication alone or an enlarging adenoma, requiring frequent pituitary imaging. Furthermore, in addition to possible resultant skin hyperpigmentation due to excess ACTH, endogenous cortisol elevations may ultimately overwhelm the receptor antagonism. The authors of one report used the drug as a last resort in an extremely ill patient with an ACTH-secreting macroadenoma and profound metabolic disturbances, psychosis, and cardiomyopathy, obtaining successful resolution of these symptoms (including significant reversal of heart failure). Notably, however, spironolactone was needed to manage resultant hypokalemia, attributed to the unhindered mineralocorticoid activity of excess cortisol.

Overall, the most well-studied and efficacious pharmacological therapies include the adrenal enzyme inhibitors ketoconazole, aminoglutethimide, metyrapone, and etomidate (intravenously administered) as well as the adrenolytic agent mitotane, which additionally has inhibitory effects on several adrenal enzymes. Figure 1 provides a summary of the effects of these medications on adrenal steroid synthesis. Most often, therapy is initiated with ketoconazole. If cortisol levels are not adequately controlled, metyrapone and/or aminoglutethimide can be added to the medication regimen as needed (Fig. 2). Such combinations of these medications are quite common and allow usage of potential synergistic effects among them while limiting side effects that would occur if exceedingly high doses of one medication were used. One drawback to adrenal enzyme inhibitors is the need to increase doses with time because the relative decrease in cortisol they cause can stimulate further ACTH secretion. Additionally, the side effects of these medications (Table 1) may ultimately limit their use.

At any juncture, an alternative for patients becomes bilateral laparoscopic adrenalectomy. The authors of a recent publication showed that during a 3-month to 10-year follow-up period, 79.4% of patients had undetectable serum cortisol levels whereas the procedure itself was asso-
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**Neuromodulatory**

**NOT EFFECTIVE**

- Bromocriptine
- Cyproheptadine
- Octreotide
- Valproate

**Adrenal Enzyme Inhibitors**

1. Ketoconazole 200 mg TID
   - If unsuccessful
2. Increase Ketoconazole up to 400 mg TID
   - If unsuccessful, add
3. Metyrapone 250 mg TID
   - If unsuccessful
4. Increase Metyrapone up to 4 g/day
   - If unsuccessful, add
5. Aminoglutethimide 250 mg TID
   - If unsuccessful
6. Consider Mitotane

**Glucocorticoid Receptor Antagonism**

**UNDER INVESTIGATION**

- Mifepristone

Fig. 2. Medical management of Cushing disease. TID = three times a day.

Liver function should be closely monitored during ketoconazole use considering the drug’s ability to cause idiosyncratic reversible hepatic dysfunction and elevation of aminotransferase levels. These are likely to be dose-dependent effects because the prevalence of overt hepatitis decreases in patients treated with lower doses of the drug for onychomycosis (2.9% prevalence for a daily dosage of 200 mg).

Therapy should be promptly ceased in patients with hepatitis, but in patients with asymptomatic anicteric aminotransferase elevations, the decision is at the physician’s discretion, although the only investigators who have advocated continuing the drug were those using it at lower doses for onychomycosis.

In addition to hepatic side effects, nausea, vomiting, headache, and sedation may occur. Other noted side effects of this medication include decreased libido and impotence, probably owing to its inhibitory effects on 17α-hydroxylase and 17,20-lyase, vital enzymes for the synthesis of androgens as shown in Fig. 1. Teratogenicity contraindicates use of this medication in pregnant women. Significant medication interactions may occur due to ketoconazole’s potent inhibitory effects on the cytochrome P450 enzymes, particularly CYP3A4, CYP2C9, and CYP1A2. The CYP3A4 substrates include most benzodiazepines aside from lorazepam; many calcium channel blockers such as nifedipine and verapamil; 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, aside from pravastatin and fluvastatin, and pimozide, generally contraindicating their use. The CYP2C9 substrates include fluoxetine, glipizide, losartan, montelukast, phenytoin, and warfarin. The CYP1A2 substrates include mirtazapine, ropinirole, and theophylline. Sildenafil, tadalafil, and vardenafil concentrations may also be increased. The CYP3A4 inducers such as aminogluthethamide, carbamazepine, and phenytoin may decrease ketoconazole levels, and as ketoconazole absorp-

Associated with a 0% morality rate and 10.3% morbidity rate. Such patients should, however, be monitored closely for the development of Nelson syndrome. In the aforementioned study the investigators reported that 25.7% of patients had serum ACTH levels greater than 300 pg/ml, 8.6% had magnetic resonance imaging evidence of tumor growth, and 11.1% had clinically significant hyperpigmentation.

**Ketoconazole Therapy**

Ketoconazole, the initial drug of choice, is administered at initial doses of 200 mg (two to three times daily) with dose adjustments based on 24-hour urine free cortisol levels. Maintenance doses are often at 400 mg (two to three times daily). Its fast onset of action allows monitoring of serum cortisol within as little as 1 day of use to observe its efficacy and adjust its dosage. Although its strongest effects are on 17,20-lyase, it additionally blocks adrenal steroid synthesis by preventing cholesterol side chain cleavage and 17α-hydroxylase.

Though controversial, it is generally accepted that it does not in fact block human 11α-hydroxylase.

The authors of a metaanalysis of eight trials involving a range of 400 to 1200 mg of ketoconazole daily in patients with Cushing disease revealed an average remission rate of 70% (range 25–93%). Across these studies the most common side effect was hepatotoxicity, observed at an overall rate of 12%. Notably, authors of the study with the most cases (34 patients) and longest follow-up period (up to 3 years) reported 26 patients (76%) with normalized cortisol levels when they used daily doses of ketoconazole ranging from 400 to 800 mg. This percentage was further increased to 93% (26 of 28) when patients who initially discontinued use of the medication were excluded.
This limitation can be addressed—hydroxylase. Unfortunately, the re-

Cholestasis and bone marrow

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21

of urinary cortisol levels.

of patients experienced an ef fective short-term response.

Mitotane is often started at 250 to 500 mg nightly with

slow escalation of the dose to 4 to 12g/day. Mitotane

inhibits 11α-hydroxylase, 18-hydroxylase, 3α-hydroxy-

lase, hydroxysteroid dehydrogenase, and several chole-

totane, another 11α-hydroxylase inhibitor, presumably
due to its inhibitory effect on other enzymes involved in adren-

androgenic and mineralocorticoid synthesis. Other com-

side effects of metyrapone include edema, nausea, and

vomiting.

Despite increased ACTH secretion, the inhibitory effect

of metyrapone overcomes the increased drive to produce
cortisol and has shown efficacy over an extended period in

case reports—one including a 13-year-old boy receiving

a 2-g regimen of metyrapone for 4 years. All cushingoid

features disappeared and the patient grew 23 cm.2 In a larg-
er study including 53 patients with Cushing disease, the

authors reported effective short-term mean serum cortisol

level control (≤ 400 nmol/L) in 75% of patients with effect-

ive long-term control in 83% of the 24 patients who were

given metyrapone (mean 2250 mg/day, median 27 months)

following pituitary irradiation.31

Of note, however, the criterion for “cortisol control” in

the latter study was a mean serum level less than 400

nmol/L. When the more accepted, stringent criterion of

Orth and Liddle23 is applied (280 nmol/L cutoff), only 19%
of patients experienced an effective short-term response.

Overall, Orth25 concluded that metyrapone is only useful as

adjunctive treatment for Cushing disease. Of note, mety-

rapone is not available in pharmacies but can be provided

for compassionate use by contacting the manufacturer di-

rectly.

Aminoglutethimide Therapy

Aminoglutethimide, often used at a dose of 250 mg two
to three times daily, prevents conversion of cholesterol to pregennolone.25 In an original study of 33 patients with

Cushing disease receiving a 250-mg dosage of aminoglu-

tethimide three times daily, the authors noted a clinical

and biochemical remission rate of 42%, the latter defined

as a 50% reduction in morning serum cortisol levels or a

return to normal limits.17 Unclear, however, was the dura-
tion of follow-up for these patients, and, in the authors’

extended discussion of a representative case of aminoglu-
tethimide therapy for Cushing disease, the patient ulti-

mately required bilateral adrenalectomy for continued bio-

chemical remission.17 Indeed, it is generally accepted that

aminoglutethimide is, overall, not efficacious as monother-

apy because its effect is generally not strong enough to nor-

malize urinary cortisol levels, likely owing to, in part, the

ability of resultant elevated ACTH to overwhelm its effect.7

Thus, it is now most often used as an adjunct to

metyrapone, with one study showing efficacy up to 1 year

when the drug was administered at 500 to 750 mg per day

in conjunction with 2 g of metyrapone daily in four of six

patients;2 the other two patients discontinued the drug due
to side effects. The primary side effect of this medication is

a generalized, self-limited pruritic rash that is usually man-

ageable with antihistamines without requiring drug cessa-
tion. In addition, nausea and somnolence may occur, par-
ticularly at higher doses. Other neurological side effects

include dizziness and blurred vision. As the drug blocks

thyroid hormone synthesis, hypothyroidism is a known,

albeit more rare, side effect.25 Cholestasis and bone marrow

suppression are similarly rare side effects. In addition,

aminoglutethimide is a strong inducer of several cytochrome P450 enzymes, including CYP1A2 and CYP3A4, underscoring potential medication interactions, decreasing ketoconazole levels (see above for other substrates of these enzymes). This medication

increases the metabolism of dexamethasone but not hydrocortisone, the latter is often used if steroid replace-

ment is needed.25,26

Mitotane Therapy

Mitotane is often started at 250 to 500 mg nightly with

slow escalation of the dose to 4 to 12g/day. Mitotane

inhibits 11α-hydroxylase, 18-hydroxylase, 3α-hydroxy-
lase, hydroxysteroid dehydrogenase, and several chole-

tisol side chain cleavage enzymes.10,18 At doses greater

than 4 g per day, it has adrenolytic action because its metaboli-
tes bind macromolecules in adrenal cortical cell mitochon-
dria, leading to their destruction and cellular necrosis. This

property underscores its primary use in patients with adrenocortical carcinoma.

In a study of 46 patients with Cushing disease receiving

anywhere from 4 to 12 g of mitotane per day, remission

occurred in 8 months in 38 cases (83%).15 Unfortunately,

however, in 60% of these patients relapse occurred after

the drug was discontinued, leaving only one third of patients

with long-term remission. In another study of 36 patients

undergoing adjunctive radiotherapy (4000 rad) the authors

observed clinical and biological remission in 29 patients

(81%) with 17 (47%) ceasing to undergo long-term mito-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>ketoconazole</td>
<td>reversible hepatic dysfunction, nausea, sedation, decreased libido, impotence</td>
</tr>
<tr>
<td>metyrapone</td>
<td>hirsutism, hypertension, edema, nausea</td>
</tr>
<tr>
<td>aminoglutethimide</td>
<td>rash, nausea, somnolence, dizziness, blurred vision, hypothyroidism (rare: cholestasis, bone marrow suppression)</td>
</tr>
<tr>
<td>mitotane</td>
<td>hypercholesterolemia, nausea, anorexia, confusion, gynecostasia, ataxia, vertigo</td>
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tane therapy. Four patients had no response, two had partial responses, and the other patient died of an invasive pituitary malignancy. Patients were initially started at 4 g of mitotane per day and the dose was tapered to a final dose of 500 mg twice weekly.

The efficacy of mitotane is monitored by examining morning serum cortisol levels. Once a decline is observed, prednisone or dexamethasone replacement therapy can begin as needed. Although the longer half-life of dexamethasone may make it seem to be a more attractive replacement therapy, its metabolism is increased by mitotane (as is the metabolism of fludrocortisone), requiring dose adjustments, whereas the metabolism of cortisol or prednisone has not been shown to be increased. Of note, patients who undergo medical mitotane adrenalectomy are at risk of developing Nelson syndrome if they do not receive pituitary radiotherapy.

Unfortunately, side effects of this medication may limit its use and have essentially set it as second or third line after ketoconazole. In the aforementioned studies, one group documented hypercholesterolemia as a prevalent side effect whereas another, which also used pituitary irradiation, documented anorexia, nausea, diarrhea, decreased memory, and gynecomastia. Overall, the most commonly documented drug-related side effects are nausea and hypercholesterolemia. At higher doses of the drug, neurological side effects are common, including gait ataxia, vertigo, confusion, and difficulty with language expression. Furthermore, the drug is contraindicated in pregnant women owing to teratogenicity.

**Etominate Therapy**

Etominate, a commonly used short-acting intravenous anesthetic, is an exceedingly potent inhibitor of 11α-hydroxylase as well as an inhibitor of 17α-hydroxylase at a strength comparable to ketoconazole. It essentially serves as an intravenous alternative to the aforementioned medications; however, given its sedative effects and availability in intravenous form alone, it is mainly used for acute control of hypercortisolemia. Most investigators to date have analyzed its use in hospitalized patients with neoplasms secreting ACTH. In one study in which the authors used it at a nonsedating dose of 0.3 mg/kg/hour, it normalized serum cortisol levels within 12 hours in six patients with Cushing disease.

**Conclusions**

Although medical management of Cushing disease is generally not considered a first-line option, it has exhibited adequate success as a preoperative, radiosurgical adjunct, or even as a stand-alone measure. Attempts to control ACTH levels with neurmodulators have demonstrated only limited success, but the use of adrenal enzyme inhibitors has shown some promise to date. Given its tolerability and average efficacy of 70% (range 25–93%) in trials, ketoconazole is often the initial pharmacological agent utilized. Subsequently, one may add metyrapone and/or aminoglutethimide for further control of cortisol levels. The adrenolytic agent mitotane is another alternative that is often used as a second or third choice owing to its side effects. Etomidate is a potent intravenous alternative for acute cortisol control.

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**References**


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