

Antiglucocorticoid Treatment in Depression

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Abstract

Hypercortisolism and resistance to dexamethasone suppression are common findings in major depression. The degree of hypercortisolism has been shown to be related to the severity of depressive symptoms. Adrenal cortisol secretion is known to increase in response to a wide variety of stresses, including psychological stress. Several investigators have theorized that the hypercortisolism associated with depression is a prototypical secondary stress response. Recently, investigators have begun to examine the effect of pharmacologic reduction of cortisol levels in depressed subjects. A series of small open trials and controlled trials suggest that antiglucocorticoids have antidepressant activity in hypercortisolemic depressed patients. Furthermore, findings from these trials suggest that adrenal hyperfunction associated with depression may not be a secondary epiphenomenon. This paper examines the role of hypercortisolism in major depression, the importance of accurate titration of antiglucocorticoid agents, and discusses the potential of antiglucocorticoid therapy for patients with major depression.

Background

Since the late 1960s, two well-established biochemical abnormalities in the majority of cases of major depression have been observed: hypercortisolism and resistance to dexamethasone suppression.¹ The degree of hypercortisolism in major depression has been shown to be related to more severe symptoms, such as sleep disturbance, psychomotor disturbance, weight loss, decreased energy, anxiety, delusions, decreased memory, and cognitive impairment.^{2, 3, 4, 5, 6} Several investigators have theorized that the hypercortisolism observed in depressed patients is secondary to the "stress" of depression.⁷

Adrenal cortisol secretion is known to increase in response to a wide variety of stresses such as surgery, trauma, and infection.

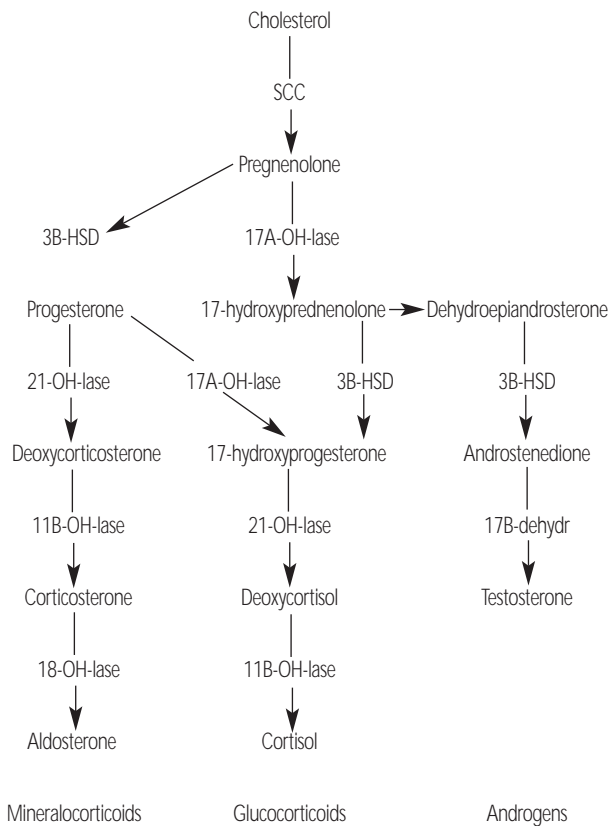
Individuals with severe primary or secondary adrenocortical insufficiency must increase their exogenous intake of cortisol in response to such stress. Failure to do so may result in the development of an adrenal crisis. Similarly, it can be argued that patients with severe hypocortisolemia should increase their exogenous cortisol intake in response to significant psychological stress. Jefferies has noted that failure to do so may result in fatigue, malaise, aches similar to that experienced during influenza infection, nausea, vomiting, high fever, low blood pressure, and shock – the signs and symptoms which characterize an adrenal crisis.⁸ This suggests that the hypercortisolism associated with the stress of depression may be a necessary biological adaptation.

However, it is also possible that the hypercortisolism associated with depression perpetuates or exacerbates depression. Cortisol secretion may be excessively elevated beyond levels necessary to protect the individual from the stress of depression. Indeed, in Cushing's syndrome, depression is common and usually remits after the hypercortisolemia is treated.⁹ Similarly, the pharmacologic administration of glucocorticoids to medically ill patients is also associated with neuropsychiatric symptoms such as emotional lability, anxiety, depression, and cognitive impairment.¹⁰ In order to determine whether the hypercortisolism of major depression plays a pathophysiologic role in some individuals with major depression, it is necessary to lower cortisol levels in depressed patients and measure the effect of such an intervention.

Three medications have been used for the pharmacological reduction of hypercortisolism in Cushing's syndrome: metyrapone, aminoglutethimide, and ketoconazole. Metyrapone is an 11-beta hydroxylase inhibitor and consequently blocks the conversion of 11-deoxycortisol to cortisol (Figure 1). Aminoglutethimide inhibits cholesterol side-chain-cleavage enzyme thus decreasing the production of all adrenal steroids,

including cortisol. Ketoconazole, in doses over 400 mg per day, interferes with several cytochrome P-450 enzymes, including cholesterol side-chain-cleavage enzyme, 11-beta hydroxylase, and 17-alpha hydroxylase, with the net effect of blocking cortisol biosynthesis.^{11, 12} Ketoconazole also blocks peripheral glucocorticoid receptors.^{11, 12}

exclaimed that 'my head feels clear for the first time in months' (almost the same words used by several other responders). This first patient made such rapid progress that she was able to leave hospital on the sixth day of therapy and to be followed as an outpatient; after eight weeks the medication was discontinued. Cortisol levels and dexamethasone suppression had returned to normal by the end of treatment; she has never relapsed."



SCC = Cholesterol side chain cleavage enzyme
 3B-HSD = 3-beta-hydroxysteroid dehydrogenase
 11B-OH-lase = 11-beta-hydroxylase
 17A-OH-lase = 17-alpha-hydroxylase
 17B-dehydr = 17-beta-dehydrogenase
 18-OH-lase = 18-hydroxylase
 21-OH-lase = 21-hydroxylase

Figure 1. Steroid synthesis pathway.

Evidence that Supports Antiglucocorticoid Therapy in the Treatment of Depression

Despite the availability of antiglucocorticoid agents, few studies have reported the effect of pharmacologically lowering cortisol levels in depressed patients. A description of antiglucocorticoid therapy in major depression comes from a review of such therapy by Murphy:¹³

"...extreme hypercortisolism and resistance to dexamethasone were observed in a thin, suicidally-depressed young woman with low normal blood pressure and no signs of Cushing's syndrome.¹⁴ She had been admitted on three occasions during the previous year for attempted suicide and had failed to respond to many antidepressants given. Her response to oral aminoglutethimide (Cytadren) and cortisol (hydrocortisone, Cortef) was dramatic. After three days of therapy she

In an open trial, Wolkowitz treated 10 out-patients diagnosed with various subtypes of depression (8 unipolar, 2 bipolar, none of whom exhibited psychotic symptoms) with ketoconazole for 3-6 weeks in an attempt to lower their serum cortisol levels.¹⁵ All patients had at least 1 of 2 pretreatment cortisol values above 12 µg/dl (measured at 4 p.m.) and were medication-free for 2.5 months prior to the study. The ketoconazole dose employed was 400-800 mg on the basis of drug tolerance. Three patients dropped out due to side effects or illness. Of the 7 that remained, serum cortisol levels and depression ratings were decreased.

In another open trial, Ghadirian and colleagues examined the effects of antiglucocorticoid therapy in antidepressant-resistant patients with severe psychotic depression (n=9) or non-psychotic depression (n=11).¹⁶ Patients were treated with aminoglutethimide or ketoconazole with or without metyrapone for 8 weeks. A pre-study medication washout period of 1 week for tricyclic antidepressants and 21 days for selective serotonin reuptake inhibitors was undertaken, during which time patients could use chloral hydrate for insomnia and benzodiazepines for anxiety. A flexible medication schedule was used: patients were started on either aminoglutethimide or ketoconazole. The medication was increased every 4-7 days until the Hamilton Depression Rating Scale (HDRS) score fell below 15. The medication was switched (ketoconazole to aminoglutethimide or *vice versa*) if hepatic enzyme concentrations were elevated 2 times above the upper limit of normal, if side effects interfered with treatment, or if there was an inadequate response to treatment. Metyrapone was added to the regimen if improvement was still unsatisfactory. Of the 17 patients who completed the study, 11 patients responded completely as assessed by a decrease of greater than 50% in the HDRS score to less than 15. Two of the patients responded partially and non-psychotics did better than psychotics.

In another open trial, Thakore and Dinan treated 8 non-obese, otherwise healthy in-patients suffering from depression (5 melancholic, 3 psychotic) with ketoconazole for 4 weeks.¹⁷ Six of the patients were on other medications whereas 2 were drug-free for 6 weeks before the study. Patients were started on 200 mg of ketoconazole and the dose was increased to 400-600 mg over 4 weeks, on a weekly basis, until an adequate response was observed. Five patients recovered from their depression, while the other 3 had decreases in their HDRS scores by less than or equal to 50%.

In a placebo-controlled single blind crossover study, O'Dwyer and colleagues treated 8 in-patients diagnosed with major depression, who were otherwise healthy, with metyrapone and hydrocortisone or placebo for 2 weeks.¹⁸ Six of the patients were medication-free while the others had been on a constant treatment regimen that was not altered during the previous 4

weeks. A replacement dose of 30 mg of hydrocortisone was administered as a divided 7.5 mg dose qid. The metyrapone dose was titrated from 500 mg qid to 1 gram qid against plasma cortisol in order to keep cortisol within the physiological range. Six of the 8 patients had significant reductions in their depressive symptoms.

Recently, in a double-blind placebo controlled study, Wolkowitz and colleagues treated 20 medication-free, depressed patients, who were otherwise healthy, with ketoconazole or placebo for 4 weeks.¹⁹ Thirteen of the patients were resistant to prior antidepressant therapy; 7 were never treated before with antidepressants. Ketoconazole was given in doses of 400-800 mg. If the dose was greater than 400 mg, it was given twice daily. The medication was titrated blindly according to subject tolerance. In the depressed patients with hypercortisolism, ketoconazole therapy was associated with improvement in depression ratings. Ketoconazole did not improve depression in non-hypercortisolemic patients. Furthermore, cortisol levels were not decreased in the ketoconazole treated group. The investigators noted that the significance of these findings was tempered by the small number of hypercortisolemic patients who were randomized to ketoconazole treatment (n=3), the relatively short duration of the treatment trial, and the simple method used to assess cortisol status (single reading taken at 4 p.m.). Wolkowitz and colleagues concluded that antiglucocorticoids have antidepressant activity in hypercortisolemic depressed patients and that adrenocortical dysfunction has a causal role in some depressed patients.

The studies described above suffer from their small sample size (n = 8 - 20), relatively short duration (2 to 8 weeks), and the fact that 3 of the 5 studies were open trials. Nonetheless, at this stage, evidence from these trials suggests that antiglucocorticoid treatment may be beneficial to many patients who suffer from depression.

Discussion

Could depression be caused or exacerbated by an inappropriate "functional" hypercortisolism? In her review of antiglucocorticoid therapies in major depression, Murphy argues that, "several lines of evidence lead one to suspect that cortisol itself may not be the important entity in causing depression."¹³ Her reasons are the following:

1. Cortisol is not elevated in all depressed patients.
2. Euphoria occurs more often than depression following glucocorticoid administration.
3. In a study by Murphy and colleagues, the Hamilton Depression scores dropped rapidly although 8 a.m. cortisol levels remained high.²⁰
4. Giving cortisol at the same time as steroid-synthesis inhibitors did not appear to affect the results.^{18, 20}

Although it is possible that other adrenal steroids such as androgens, which are suppressed by antiglucocorticoid therapy, may contribute to depression, the above arguments are not necessarily convincing if some pertinent endocrinological concepts are kept in mind.

First, adrenal cortisol secretion fluctuates throughout the day in response to waking (namely, its diurnal rhythm), stress, and several other environmental stimuli such as eating and sunlight. This has undoubtedly resulted in relatively broad "normal" laboratory ranges for cortisol. Some depressed individuals with cortisol levels within the broad "normal" range might therefore be mildly hypercortisolemic. Furthermore, the Diagnostic and Statistical Manual (DSM-IV) diagnosis of depression is a phenomenological diagnosis. It is not prudent to assume that hypercortisolism, *or any specific biochemical abnormality* underlies *all* major depression. If some individuals with major depression do not have hypercortisolism and simply have another underlying abnormality contributing to their depressive symptomatology, this does not imply that in those depressed individuals with hypercortisolism, the hypercortisolism is not of pathophysiological significance. This is confirmed by the above-mentioned study of Wolkowitz and colleagues.¹⁹

Second, although glucocorticoids given exogenously in supraphysiological dosages cause euphoria more than depression, in many patients the euphoria typically proceeds to depression if steroid therapy is continued. Furthermore, with the exception of adrenal insufficiency, hydrocortisone and cortisone acetate (a pharmacologic precursor of hydrocortisone) are seldom used as steroid therapies. It should not be presumed that synthetic cortisone derivatives such as prednisone, prednisolone, or dexamethasone have the same neuroendocrinological effects as the normal hormone cortisol.

Third, although the Hamilton Depression scores dropped rapidly while the 8 a.m. cortisol levels remained high, some of the patients in this study conducted by Murphy and colleagues were placed on ketoconazole.²⁰ As mentioned above, ketoconazole blocks glucocorticoid receptors and therefore serum levels of cortisol might tend to overestimate post-receptor tissue levels.^{11,12} Furthermore, while single morning levels of cortisol were high, it is unclear as to what the level of cortisol secretion was throughout the remainder of the day, which may have been much lower than before treatment. In the same review article Murphy states, "Cortisol levels are of little use because of the feedback mechanism, so that there is a great fluctuation with time of sampling."¹³ Serial blood or salivary cortisol levels throughout the day would have been more appropriate.

Finally, when Murphy²⁰ and O'Dwyer¹⁸ gave exogenous steroids to their patients in conjunction with cortisol biosynthetic inhibitors, the dosages of cortisol were approximately subreplacement (20 mg at bedtime) and replacement (7.5 mg four times daily), respectively. The dosages of steroid were not, however, in a typical replacement schedule that mimics the diurnal endogenous secretion of cortisol (i.e., cortisol highest shortly after waking and lowest in the evening). It is therefore difficult to draw conclusions as to the effect of the above replacement therapies on endogenous cortisolemia. It is possible that while the cortisol biosynthetic inhibitors down-regulated endogenous hypercortisolemia, the exogenous dose of steroid partially or near completely replaced remaining endogenous cortisol resulting in a net reduction in serum cortisol. It is also possible that the exogenous dose of cortisol protected the patients from mild to moderate adrenal insufficiency secondary to over-titration of

antiglucocorticoid medication. A mild to moderate adrenal insufficiency would likely not be detectable on laboratory testing as the physiologic range for cortisol is large.

Future Directions

Double blind randomized controlled trials with large sample sizes are required in order to determine the effectiveness of treating depressed patients with antiglucocorticoids. In addition, measurements of pre- and post-treatment serum cortisol levels at several times throughout the day, as well as 24 hr urinary cortisol clearance are necessary. These measures will hopefully help establish hypercortisolemic criteria that would predict which depressed individuals are likely to benefit from antiglucocorticoid therapy. Given that multiple investigations of cortisolemia are expensive and impractical, it will be necessary to develop surrogate markers of hypercortisolism. As an example, dehydroepiandrosterone (DHEA), an adrenal androgen with a longer half-life than cortisol, would be useful as it is subject to less fluctuation in serum levels. This steroid may therefore serve as an effective marker for increased adrenocortical (and cortisol) output. The investigation of other adrenal steroids in this manner may also help to delineate which patients are likely to benefit from such therapy.

Titration methods in antiglucocorticoid therapy need to be carefully explored. The over-titration with antiglucocorticoid drugs may result in mild to moderate hypocortisolemia which may worsen depression or not improve the depression as much or as quickly possible. This important fact has received little attention in the current literature discussing antiglucocorticoid therapy in depression. Indeed, patients with untreated adrenal insufficiency often have psychiatric symptoms including depression (20-40%) manifested by apathy, poverty of thought, and lack of initiative. As well, psychosis (20-40%) manifested by social withdrawal, irritability, negativism, poor judgement, agitation, hallucinations, paranoid delusions, and bizarre or catatonic posturing is also common in hypocortisolemic patients.²¹ These psychiatric symptoms occur early in the disease and may pre-date other physical findings. This suggests that the mild to moderate hypocortisolism of early adrenocortical insufficiency has psychiatric implications. Similarly, mild to moderate hypocortisolemia resulting from over-titration of antiglucocorticoid therapy may also have psychiatric implications.

As serum cortisol levels are generally of little value in monitoring subtle degrees of adrenal insufficiency (or excess), titration using antiglucocorticoid drugs should be based on remission of depressive symptomatology and should proceed very slowly. The subsequent administration of subreplacement dosages of cortisol may have the added benefit of protecting the patient from small degrees of cortisol insufficiency and may, consequently, allow for more rapid dose titration of antiglucocorticoid medication. In the future, surrogate markers of hypercortisolism may also play a role in accurate titration of antiglucocorticoid therapy.

The use of current glucocorticoid inhibitors are not without hazards. Over-titration with antiglucocorticoid medication, without concomitant glucocorticoid replacement, may result in

severe adrenal insufficiency with catastrophic results. Antiglucocorticoid side effects are also important. Ketoconazole, in antifungal doses (generally less than 400 mg per day), is associated with a 10% incidence of transient increases in liver enzymes with hepatic injury occurring in less than 1% of patients.¹² Pruritis and gastrointestinal reactions are also common side effects. Side effects from metyrapone include hirsutism, dizziness, edema, hypokalemia, nausea, and rash, though these side effects were reported in patients treated for Cushing's syndrome.²² If antiglucocorticoid therapy proves to be efficacious, the development of other antiglucocorticoid pharmaceuticals with lower toxicity profiles would be desirable.

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