Antiglucocorticoid Treatment of Depression: Double-Blind Ketoconazole

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Background: *Hypercortisolemia is frequently observed in major depression but its pathophysiologic significance is unknown. In patients in whom hypercortisolism contributes to depressive symptomatology, antiglucocorticoid agents should have antidepressant effects.*

Methods: *Twenty medication-free depressed patients (eight of whom were hypercortisolemic and twelve of whom were not) received either the cortisol biosynthesis inhibitor, ketoconazole (400–800 mg/d p.o.) or placebo for 4 weeks in a double-blind manner, and behavioral ratings were performed weekly.*

Results: *Ketoconazole, compared to placebo, was associated with improvements in depression ratings in the hypercortisolemic, but not in the non-hypercortisolemic patients. The hormonal changes seen (decreased dehydroepiandrosterone and testosterone levels and increased pregnenolone and pregnenolone-sulfate levels) are consistent with enzymatic blockade of C17,20-lyase, 11-hydroxylase, and 17-hydroxylase. Ketoconazole was generally well tolerated with no occurrence of significant side effects or laboratory abnormalities.*

Conclusions: *This small-scale double-blind study suggests that antiglucocorticoids have antidepressant activity in hypercortisolemic depressed patients. The data are consistent with a causal role of adrenocortical dysfunction in some depressed patients and suggest the need for larger-scale trials.* Biol Psychiatry 1999;45:1070–1074

Key Words: Cortisol, antiglucocorticoid, ketoconazole, depression, antidepressant, dehydroepiandrosterone (DHEA)

Introduction

Hypercortisolism, either basally or following dexamethasone administration, has been repeatedly demonstrated in a subgroup of patients with major depression (c.f., review by Murphy 1991), although it remains uncertain whether the hypercortisolism is an epiphenomenon or whether it directly contributes to the depression. In patients in whom hypercortisolemia contributes to depressive symptomatology, drug treatments that directly lower corticosteroid activity should have antidepressant efficacy. Several studies recently applied this strategy to patients with major depression with generally favorable results (Ravaris et al 1988; Murphy et al 1991, 1998; Wolkowitz et al 1993; Amsterdam et al 1994; Anand et al 1995; O'Dwyer et al 1995; Sovner and Fogelman 1996; Thakore and Dinan 1995; Iizuka et al 1996). These studies, however, have all been either case reports or single-blind or open-label trials. The current report presents data from the first double-blind trial (other than the single case report of Anand et al 1995) of antiglucocorticoid drug treatment of major depression. In addition to assessing efficacy, we sought to clarify the predictive value of baseline hypercortisolemia on treatment response.

Methods and Materials

Twenty outpatients with DSM-IV major depression (12 women and 8 men; mean age 46.9 ± 14.0 (SD) years) participated after granting informed consent. All subjects had baseline 21-item Hamilton Depression Rating Scale (HDRS) ratings of ≥17, had been medication-free for a minimum of 6 weeks, and were medically healthy. These were different subjects than those studied in our previous open-label trial (Wolkowitz et al 1993); most had been previously resistant to, or intolerant of, other antidepressant medication ($n = 13$), or else had never previously been treated with antidepressant medications ($n = 7$).

Subjects who were either hypercortisolemic, as defined by our laboratory normal range (1600 hr serum cortisol level > 10 μg/dL on an average of two separate afternoon blood samples), or eucortisolemic (≤10 μg/dL) were randomized to receive identically packaged ketoconazole (400–800 mg/d p.o. [divided b.i.d. or, for doses above 400 mg/d, t.i.d.]; average dose = 655.6 ± 181.1 mg/d) or placebo in a double-blind manner for 4 weeks. No other medications were allowed during the study period. Doses were individually titrated by a researcher blind to drug condition according to subject tolerance of the medication.

Twelve eucortisolemic and eight hypercortisolemic patients were enrolled. Six of the eucortisolemic patients received pla-

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Table 1. Double-blind ketoconazole treatment of depression: Change in depression ratings

	Hypercortisolemic				Eucortisolemic				ANOVA (cortisol status × drug group)	
	Keto (n = 3)		Pla (n = 5)		Keto (n = 6)		Pla (n = 6)			
Rating Scale	Base	End	Base	End	Base	End	Base	End	F (1,16)	$p \leq$
Hamilton Depression Rating Scale (HDRS)	26.7 ± 6.4	14.0 ± 5.6	23.0 ± 1.9	21.0 ± 4.2	23.5 ± 4.1	20.2 ± 5.2	21.7 ± 2.8	15.5 ± 7.2	5.68	.03
Bunney-Hamburg Global Depression	7.3 ± 2.5	3.7 ± 2.5	7.6 ± 0.9	6.8 ± 1.8	7.7 ± 1.6	7.0 ± 2.7	6.5 ± 1.6	4.0 ± 2.0	5.21	.04
Symptom Checklist-90 (SCL-90)	215.0 ± 77.3	159.0 ± 43.2	205.8 ± 27.8	195.0 ± 33.4	189.3 ± 32.5	175.8 ± 32.6	204.3 ± 40.8	150.5 ± 10.9	6.58	.03
Beck Depression Inventory (BDI)	23.0 ± 9.5	11.7 ± 5.5	25.0 ± 7.8	22.4 ± 10.9	22.0 ± 4.3	18.3 ± 4.2	24.3 ± 4.8	16.8 ± 6.3	1.68	NS

Values are means ± S.D.
Keto = ketoconazole; Pla, placebo.

cebo and six ketoconazole. Five of the hypercortisolemic patients received placebo and three ketoconazole. At baseline and at the end of each week of the study, subjects were rated with the 21-item Hamilton Depression Rating Scale (HDRS), Bunney-Hamburg (BH) Global Depression Ratings, Beck Depression Inventory (BDI), and Symptom Checklist (SCL)-90 and had blood drawn at 1600 hr for assay of steroid hormones (cortisol, dehydroepiandrosterone [DHEA], DHEA-sulfate [DHEA-S], pregnenolone [P], P-sulfate, estradiol, and testosterone), sodium, potassium, alkaline phosphatase, AST, ALT, and total bilirubin. Additionally, at the end-of-study visit, blood was drawn for serum ketoconazole levels. Subjects were instructed to take their regular morning study medication dose but not their afternoon dose (if applicable) on the days of venipuncture.

Statistics

Data were analyzed by two-factor ANOVA (drug treatment [ketoconazole vs placebo] × baseline cortisol status [hypercortisolemic vs eucortisolemic]) with repeated measures (time). Changes in behavioral ratings (week 4 minus baseline) were correlated with changes in the biochemical measures by Pearson product-moment correlations. For correlational analyses, behavioral rating change was assessed using only the HDRS to limit Type I errors due to multiple testing of the hypothesis. All probability values are for two-tailed tests.

Results

Behavioral Results

Results are presented in Table 1. Whereas the main effects of drug condition and of baseline cortisol status were not significant for any of the behavioral measures, interaction effects (drug condition × baseline cortisol status) were significant for HDRS, BH Global Depression, and SCL-90 ratings. Changes in BDI ratings were in the hypothesized direction (effect size = .7) but were not statistically significant. In each significant interaction, ketoconazole was superior to placebo in the hypercortisolemic but not in the eucortisolemic group. Post hoc within-groups analyses of HDRS scores revealed a significant advantage of ketoconazole over placebo in the hypercortisolemic group ($F = 9.51$, df = 1,6, $p < .03$) with no significant advantage of either treatment in the eucortisolemic group ($F = .53$, df = 1,10, ns). Ketoconazole-associated improvements in HDRS ratings averaged 48% in the hypercortisolemic group (range: 36–58%) as opposed to 6.6% (range: minus 20–36%) for placebo in the same group. Ketoconazole-associated improvement in HDRS ratings in the hypercortisolemic patient group was progressive and almost linear over the 4 week course of the study and showed no sign of plateauing. There were no significant main or interactive effects for gender.

Table 2. Ketoconazole and placebo effects on 1600 hr serum steroid hormone levels[a]

Biochemical measure (normal range)	Drug condition	Baseline	End of Week 4	$F_{1,16}$	$p \leq$
Cortisol (5–10 μg/dL)	Ketoconazole	8.8	8.7		
	Placebo	10.4	9.9	.21	n.s.
DHEA[b]	Ketoconazole	1.26	.50		
	Placebo	1.36	1.05	11.29	.005
DHEA-S[c]	Ketoconazole	706.04	477.20		
	Placebo	906.90	806.76	.06	n.s.
Pregnenolone[d]	Ketoconazole	0.47	.69		
	Placebo	0.42	.30	4.80	.05
Pregnenolone sulfate[e]	Ketoconazole	16.85	138.02		
	Placebo	13.89	13.80	12.55	.003
Estradiol[f]	Ketoconazole	71.22	63.97		
	Placebo	59.91	80.32	2.15	n.s.
Testosterone[g]	Ketoconazole	235.06	117.55		
	Placebo	172.59	213.18	4.98	.05

[a]Values are means. Analyses of variance are based on all weekly values.
[b]Adults: 1.6–8.0 ng/mL; post-menopausal: 0.5–4.0 ng/mL.
[c]Male: 1500–4400 ng/mL; female: 700–4300 ng/mL; post-menopausal: 110–610 ng/mL.
[d]Male: 0.3–1.8 ng/mL; female: 0.5–6.0 ng/mL; post-menopausal: 0.05–1.0 ng/mL.
[e]Male: 27–80 ng/mL; female: n.s. data.
[f]Male: 10–60 pg/mL; female: 30–300 pg/mL; post menopausal: <150 pg/mL.
[g]Male: 300–1000 ng/dL; female: <100 ng/dL.

Biochemical Results

Steady state plasma ketoconazole levels at the end-of-study visit in the ketoconazole group averaged 5.47 ± 2.50 μg/mL (range = 1.9–9.6 μg/mL). Plasma ketoconazole levels were not significantly correlated with antidepressant response ($r = 0.18$; ns).

Ketoconazole had no significant effect on serum cortisol levels, although patients with higher cortisol levels at baseline had greater decreases in serum cortisol levels with ketoconazole treatment ($r = -.95$, $p = .0001$). Post hoc within-groups analyses revealed no significant change in serum cortisol levels in either the ketoconazole or the placebo-treated group. Ketoconazole significantly decreased serum DHEA and testosterone levels, and significantly increased serum pregnenolone and pregnenolone-sulfate levels (Table 2). Finally, ketoconazole had no significant effect on liver function tests or electrolytes, with the exception of serum AST, which showed a statistically significant, but clinically irrelevant, decrease (19.7 to 15.9 U/L, $p < .02$).

Ketoconazole-associated decreases in serum cortisol levels were not significantly correlated with decreases in HDRS total ratings ($r = .45$, $p = .21$) or with decreases in the Cognitive Disturbance ($r = .50$, $p = .15$) and Anxiety-Somatic ($r = .64$, $p < .08$) HDRS subscale ratings, although relationships were all in the hypothesized direction. However, treatment-associated decreases in serum DHEA levels were significantly correlated with decreases in HDRS ratings ($r = .89$, $p = .007$).

Discussion

In this double-blind pilot study, ketoconazole had significant observer-rated antidepressant effects in a subgroup of patients with major depression; the antidepressant effect was confined to patients with baseline hypercortisolemia. The significance of this finding is tempered by the small number of hypercortisolemic patients who were randomized to ketoconazole treatment ($n = 3$), the relatively short duration of the treatment trial (4 weeks) and the simple method used to assess cortisol status ("spot" 1600 hr blood levels). The present data can not address whether additional patients might have eventually responded with a longer treatment trial, with higher ketoconazole doses, or with the addition of other antiglucocorticoid agents, as reported by Murphy et al 1998.

Antiglucocorticoid-associated antidepressant effects are consistent reports in patients with Cushing's syndrome (reviewed in Murphy and Wolkowitz 1993; Reus et al 1997) and with the open-label, case study or single-blinded reports of antidepressant effects in some depressed patients (cited above). The apparent specificity of antidepressant effects for the hypercortisolemic group in the present study accords with the a priori mechanistic hypothesis that drugs like ketoconazole have antidepressant effects by interfering with the depressogenic effects of elevated corticosteroid levels. Indeed, decreases in corticosteroid activity with an accompanying up-regulation of central corticosteroid receptors (thereby increasing their sensitivity to negative feedback), may be a prerequisite for

successful and long-lasting antidepressant response (Holsboer and Barden 1996; Ribeiro et al 1993).

Although the antidepressant effect in this study was confined to the hypercortisolemic group, we failed to show a significant decrease in 1600 hr serum cortisol levels with ketoconazole. This was not attributable to insufficient ketoconazole doses, since the plasma ketoconazole levels achieved in this study were well within or above the range necessary to inhibit steroidogenesis (1–5 μg/dL), and since significant changes were noted in levels of other steroid hormones. Our failure to observe significant decreases in serum cortisol levels (as well as significant correlations between changes in cortisol levels and changes in depression ratings) differs from several (Wolkowitz et al 1993; Anand et al 1995; O'Dwyer et al 1995; Thakore and Dinan 1995; Ravaris et al 1988; Iizuka 1996), but not all (Murphy et al 1991, 1998; Raven et al 1996), prior studies. However, it is likely that more sophisticated measures of cortisol activity (e.g., 24-hour urinary free cortisol, dexamethasone suppression testing, or hourly blood sampling for cortisol), longer-term sampling of cortisol (e.g., over 8 weeks or greater), as well as use of a larger sample would provide a more accurate assessment of the effects of ketoconazole on steroid biosynthesis inhibition (Murphy et al 1998; Ravaris et al 1988).

Alternative explanations of the efficacy of ketoconazole in this population include: direct central nervous system or pituitary effects of ketoconazole, antagonism by ketoconazole of central cortisol effects without alteration of peripheral cortisol levels, and alterations in levels of adrenal or "neurosteroid" hormones other than cortisol (Murphy et al 1991; Checkley et al 1994; Raven et al 1996; Stalla et al 1989; Fahey et al 1998). According to the latter possibility, the specificity of beneficial effects in the hypercortisolemic group might be related to more general baseline adrenocortical activation, of which hypercortisolemia is merely a marker. It is worth considering, since ketoconazole robustly increased pregnenolone and pregnenolone sulfate levels, that neuroactive metabolites of pregnenolone or of its by-product, progesterone, such as allopregnanolone, may have contributed to the antidepressant effects (c.f., Uzunova et al 1998).

An unexpected finding was the significant correlation between decreases in serum DHEA levels and antidepressant response. Murphy et al (1991; 1998) also noted decreases in serum DHEA-S levels, which were correlated with antidepressant responses, in antiglucocorticoid-treated patients. It is not known if this directly implicates DHEA in the therapeutic effects of antiglucocorticoid drugs or, rather, if the declines in DHEA levels simply reflect more potent antiglucocorticoid-induced enzymatic inhibition of C17,20-lyase, followed by lesser blockade of 11-hydroxylase and of 17-hydroxylase (Sonino 1987; Murphy et al 1998). The former possibility seems unlikely since metyrapone, another antiglucocorticoid with reputed antidepressant effects, has no effect on DHEA levels (Raven et al 1996; Murphy et al 1998), and since exogenously administered DHEA reportedly has antidepressant effects of its own (Wolkowitz et al, in press).

In our study, ketoconazole was free of serious side effects. Individual subjects reported headache, nausea, or stomach cramps, but subjects and raters could not reliably guess drug condition based on side effects. In other studies, however, up to 20% of subjects have dropped out due to side effects (Wolkowitz et al 1993; Murphy et al 1998). Ketoconazole administration was also not associated with clinically significant changes in serum electrolytes or liver function tests, although individual subjects had mild, transient increases in liver transaminases. Nonetheless, ketoconazole treatment, especially at doses used in this study, has the potential to cause serious hepatotoxicity and should be considered experimental; careful and frequent monitoring for hepatotoxicity and hypoadrenalism is strongly encouraged (Sonino 1987).

If confirmed, these findings may have therapeutic as well as theoretical importance. Recent studies suggest that antiglucocorticoid drugs (alone or added to standard treatment) can benefit certain treatment-refractory patients with depression (Murphy et al 1991, 1998; Amsterdam et al 1994; Iizuka 1996), obsessive-compulsive disorder (Chouinard et al 1996), schizophrenia, and schizoaffective disorder (Wolkowitz et al 1996), and that remissions may be relatively long-lasting in certain patients even after stopping treatment, perhaps secondary to a "re-setting" of the hypothalamic–pituitary–adrenal axis (Murphy et al 1991) or an up-regulation of central corticosteroid receptors (Holsboer and Barden 1996). Larger scale trials with antiglucocorticoid drugs, employing more rigorous endocrinologic assessments, longer durations of treatment, and larger sample sizes, are encouraged.

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