

Low-Dose Hydrocortisone for Treatment of Chronic Fatigue Syndrome

A Randomized Controlled Trial

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Context.—Chronic fatigue syndrome (CFS) is associated with a dysregulated hypothalamic–pituitary adrenal axis and hypocortisolemia.

Objective.—To evaluate the efficacy and safety of low-dose oral hydrocortisone as a treatment for CFS.

Design.—A randomized, placebo-controlled, double-blind therapeutic trial, conducted between 1992 and 1996.

Setting.—A single-center study in a tertiary care research institution.

Patients.—A total of 56 women and 14 men aged 18 to 55 years who met the 1988 Centers for Disease Control and Prevention case criteria for CFS and who withheld concomitant treatment with other medications.

Intervention.—Oral hydrocortisone, 13 mg/m² of body surface area every morning and 3 mg/m² every afternoon, or placebo, for approximately 12 weeks.

Main Outcome Measures.—A global Wellness scale and other self-rating instruments were completed repeatedly before and during treatment. Resting and cosyntropin-stimulated cortisol levels were obtained before and at the end of treatment. Patients recorded adverse effects on a checklist.

Results.—The number of patients showing improvement on the Wellness scale was 19 (54.3%) of 35 placebo recipients vs 20 (66.7%) of 30 hydrocortisone recipients ($P=.31$). Hydrocortisone recipients had a greater improvement in mean Wellness score (6.3 vs 1.7 points; $P=.06$), a greater percentage (53% vs 29%; $P=.04$) recording an improvement of 5 or more points in Wellness score, and a higher average improvement in Wellness score on more days than did placebo recipients ($P<.001$). Statistical evidence of improvement was not seen with other self-rating scales. Although adverse symptoms reported by patients taking hydrocortisone were mild, suppression of adrenal glucocorticoid responsiveness was documented in 12 patients who received it vs none in the placebo group ($P<.001$).

Conclusions.—Although hydrocortisone treatment was associated with some improvement in symptoms of CFS, the degree of adrenal suppression precludes its practical use for CFS.

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CHRONIC FATIGUE syndrome (CFS) has no established cause or proven treatment.¹ It is a symptom complex that has attracted considerable attention in recent years but, on reflection, is obviously not new. In 1988, the Centers for Disease Control and Prevention (CDC) proposed

For editorial comment see p 1094.

the term *chronic fatigue syndrome* and a case definition requiring debilitating fatigue and 8 or more of 11 signs and symptoms for at least 6 months.² This definition was refined and simplified in 1994 by an international working group.³ It now requires severe, unexplained fatigue for more than 6 months that is of a new or definite onset, not due to continuing exertion, not resolved by rest, functionally impairing, and accompanied by 4 or more of the following 8 new symptoms: memory or concentration complaints, sore throat, tender lymph nodes, muscle pain, multijoint pain, a new pattern of headaches, unrefreshing sleep, and postexertional malaise lasting more than 24 hours.

Depending on the case definition applied, and how the data are acquired, the point prevalence of CFS ranges from under 0.1% to 2.6% in the primary care setting.⁴⁻⁶ Most authorities urge a limited workup for CFS, judicious use of medication to ameliorate symptoms, graded exercise, and other rehabilitative measures.^{7,8}

Efforts to identify causative factors in CFS are evolving as hypotheses are generated and tested. In the early 1980s it

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was speculated that persisting Epstein-Barr virus infection sustains the symptoms of CFS.⁹ That notion was rejected after careful epidemiologic and virologic studies and the negative outcome of a placebo-controlled trial of acyclovir.^{10,11} While a viral origin of CFS now seems remote, other hypotheses continue to be examined. A substantial body of work, for example, indicates subtle alterations in immune function affecting the numbers and activity of natural killer cells and various T-cell populations.¹²⁻¹⁴

For several years, we have pursued the hypothesis that CFS arises or is maintained by a derangement of the hypothalamic-pituitary-adrenal (HPA) axis. We were led to consider this possibility because depression is a prominent feature of CFS and patients with major depression are reported to demonstrate central nervous system-mediated activation of the HPA axis.¹⁵⁻¹⁸ We were surprised, however, to find evidence of HPA axis inactivation in CFS patients.¹⁵ While plasma cortisol levels were in the normal range, responses to cosyntropin and to ovine corticotropin-releasing hormone were blunted and the CFS patients excreted, on average, about 30% less cortisol in 24-hour urine collections than healthy, matched controls. Similar findings were made subsequently in other patient groups with atypical depressive features, fatigue, and somatic complaints such as fibromyalgia.¹⁹⁻²¹ It seemed appropriate, then, to determine whether CFS symptoms could be ameliorated through cautious hormonal supplementation to approximate normal levels and diurnal changes in cortisol levels. These are the results of our randomized, double-blind, placebo-controlled trial of low-dose hydrocortisone therapy for CFS.

METHODS

Patients

Men and women aged 18 to 55 years who met the CDC 1988 criteria for CFS,² all of whom would also meet the more liberal 1994 criteria,³ were eligible for enrollment in this trial, with the added provisos that their illness began over a period of 6 weeks or less, and that they had no contraindications to systemic steroids, such as a history of peptic ulcer disease, gastritis, hypertension, glaucoma, diabetes, or evidence of untreated tuberculosis. Patients could not have any other acute or chronic medical or psychiatric condition that required ongoing or intermittent medication. In addition, for 2 to 6 weeks before enrollment (depending on the drug) and for the duration of the study, most over-the-counter and prescription drugs except acetaminophen were proscribed. Women needed

to practice effective means of birth control and to have a negative pregnancy test at enrollment.

The diagnosis of CFS was ascertained by patient history, routine physical examination, and laboratory tests to exclude other relevant diagnoses, as recommended.^{3,7} The computerized Diagnostic Interview Schedule was used for every patient to determine lifetime and current psychiatric diagnoses based on *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)* criteria.²² Active depression that was of such severity as to warrant treatment precluded enrollment.

Study Design

This was a randomized, placebo-controlled, double-blind trial of oral low-dose hydrocortisone. All subjects provided written, informed consent to participate in a research study whose design was approved by the Institutional Review Board of the National Institute of Allergy and Infectious Diseases. Patients were admitted to the National Institutes of Health Warren Grant Magnuson Clinical Center twice, once for confirmation of study eligibility and initiation of treatment and again on completion of treatment. They were instructed to take placebo or hydrocortisone pills, equivalent to about 16 mg/m² of body surface area per day, 20 to 30 mg every morning at about 8 AM, and 5 mg every day at about 2 PM, for 12 weeks. This dosage was designed to approximate normal daily cortisol levels and their diurnal variation. Based on our prior controlled studies, this represented about a 30% net daily increase in CFS patient exposure to cortisol.¹⁵ Patient symptoms were monitored using packets of self-rating forms.

Adverse Events

Patients maintained records weekly for 12 weeks of 21 listed adverse symptoms that might be attributable to corticosteroid treatment. Biochemical evidence of steroid effects was also sought. Before administration of the study drug and at the end of treatment, tests were done to evaluate function of the HPA axis, including morning serum cortisol levels, and measurement of serum cortisol levels 1 hour after injection of cosyntropin.

Patients were instructed to request stress doses of corticosteroids should an emergency arise, and all subjects were provided Medic alert bracelets indicating this fact. Moreover, because of the theoretical possibility that 12 weeks of low-dose hydrocortisone could suppress adrenal responsiveness, any patient whose posttreatment stimulated cortisol level was lower than 276 nmol/L (<10 µg/dL) was provided (without breaking

the study code) a 6-week tapering regimen of open-label hydrocortisone treatment, after which the stimulation test was repeated.

Self-rating Instruments

Every day, beginning 2 weeks before treatment and for the duration of treatment, the patients were instructed to record their current Wellness score, a single-item global health scale, ranging from zero, representing the worst they had ever felt, to 100, representing the best they had ever felt.¹⁰ Once per week, the patients completed the Profile of Mood States questionnaire, a standardized instrument for the quantitative measure of anger, anxiety, confusion, depression, fatigue, and vigor.^{10,23} Twice before treatment and every 3 weeks thereafter, the patients completed additional standardized self-rating instruments: the Symptom Checklist-90-R,²⁴ the Sickness Impact Profile,²⁵ the Beck Depression Inventory,²⁶ and a 10-point Activity scale that we developed. All patients were also interviewed by a psychiatric specialist who administered the Hamilton Depression Rating Scale at entry to the study and again at the completion of treatment. This scale is a 17-item, observer-rated instrument that assesses the severity of symptoms commonly present in a depressive illness.²⁷

Statistical Assumptions and Analyses

Evaluation of efficacy was based primarily on changes in the Wellness score, using as end points improvement by any amount, by 5, 10, and 15 points, and the change in mean score during treatment. An individual was considered improved if he or she completed at least 10 weeks of treatment, did not discontinue treatment because of worsening symptoms or adverse reactions, and had a mean Wellness score during treatment that was higher than the mean score for a 1-week pretreatment period. All other subjects were considered not improved.

The amount of improvement in a particular scale was estimated by the difference between the treatment and pretreatment mean scores. For the Wellness score only, the amount of improvement was estimated under the assumption that 2 individuals who did not complete the study and were missing either all pretreatment or all treatment scores had the same change as the average for others who did not complete the study. Pretreatment Wellness scores were not available for 5 hydrocortisone recipients, so that improvement could not be assessed for those patients.

Seventy patients were to be enrolled, leaving 62 patients if the drop-out rate

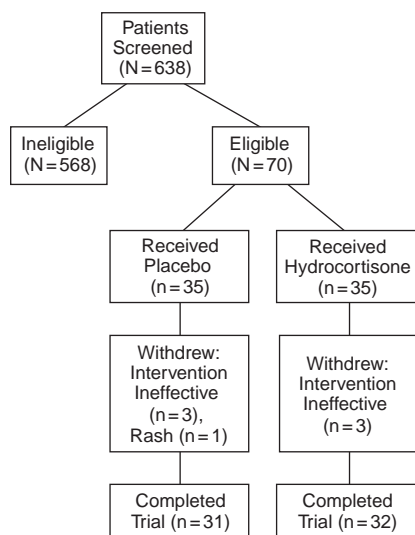


Figure 1.—A total of 638 subjects were screened and 70 were enrolled, with 35 placed in each treatment arm. Seven patients withdrew from the study, leaving 63 to comply with their assigned treatments.

was about 10%. For an underlying proportion of improvement on placebo of 50%, a study of 62 patients in 2 equal-sized groups would have 80% power to detect a treatment effect at a 2-sided .05 significance level, if the rate of improvement in hydrocortisone recipients were 83%. Randomization was done in blocks of 10 subjects.

Secondary study end points included improvement and amount of change in the other self-rating scales, adverse symptoms on treatment, and alterations in basal and cosyntropin-stimulated cortisol levels.

To measure the association between the Wellness and other scores, Spearman rank correlation coefficients were calculated for the change in Wellness scores and the changes in each of the other scores.

A χ^2 test or Fisher exact test was used to compare rates of improvement for the various instruments, baseline demographics, and adverse effects. Quantitative variables were compared using a 2-tailed Wilcoxon rank sum test with continuity correction. $P \leq .05$ was considered statistically significant. No adjustments were made for multiple comparisons. Randomization was done in blocks of 10 subjects.

RESULTS

Patient Screening and Enrollment

A total of 638 patients with chronic fatigue were screened for the study (Figure 1). Of these, 182 would not withhold proscribed medications, mostly antidepressants and nonsteroidal analgesics, and could not be enrolled—none of

Table 1.—Baseline Demographic, Endocrine, and Self-rating Data for Participants in the Chronic Fatigue Syndrome Hydrocortisone Trial

Characteristic	Hydrocortisone	Placebo	P Value
No. of subjects	35	35	
Age, mean (SD) y	36.7 (7.2)	38.3 (7.5)	.36
Sex			
Male	6	8	.55
Female	29	27	
Race			
White	34	33	.49
Black	1	0	
Other	0	2	
Period sick, mean (SD) mo	46.9 (27.3)	59.9 (31.7)	.07
Marital status			
Single	12	8	.37
Divorced	7	5	
Impaired employment*	27	24	.31
Urine cortisol excretion, mean (SD) nmol/d [μ g/24 h]	192 (95) [69.7 \pm 34.3]	187 (88) [67.7 \pm 31.8]	>.99
Serum cortisol, mean (SD) nmol/L [μ g/dL]			
Resting	425 (135) [15.4 \pm 4.9]	(397) 121 [14.4 \pm 4.4]	.32
Stimulated	877 (149) [31.8 \pm 5.4]	(825) 174 [30.9 \pm 6.3]	.79
Self-rating Wellness score, mean (SD)†	38.8 (13.3)	37.6 (15.6)	.50
Beck Depression Inventory, mean (SD)	12.0 (5.8)	9.9 (3.9)	.17
Activity scale, mean (SD)	4.7 (1.9)	5.0 (2.0)	.37
Sickness Impact Profile, mean (SD)	18.7 (8.1)	17.9 (8.6)	.55
Profile of Mood States, mean (SD)			
Anger	5.7 (6.3)	4.7 (4.4)	.74
Anxiety	8.1 (5.1)	8.0 (5.2)	.72
Confusion	10.7 (5.2)	10.0 (4.2)	.54
Depression	7.7 (5.2)	4.8 (4.3)	.09
Fatigue	19.6 (4.9)	17.8 (5.5)	.22
Vigor	7.9 (3.9)	7.3 (4.3)	.38
Symptom Checklist–90-R, mean (SD)			
General severity index	0.61 (0.4)	0.53 (0.2)	.65
Positive symptom distress index	1.7 (0.4)	1.8 (0.5)	.99
Positive symptom total	29.4 (14.7)	26.2 (10.8)	.59
Hamilton Depression Rating scale, mean (SD)‡	9.8 (4.1)	9.4 \pm 2.8	>.99
Current DSM-III-R diagnosis§			
No diagnosis	9	2	.03
Somatoform pain disorder	20	20	>.99
Somatization disorder	3	6	.31
Major depressive episode	1	1	>.99
Depression, not otherwise specified	1	3	.36
Generalized anxiety disorder	1	0	.50
Phobic disorder	2	3	.68
Posttraumatic stress disorder	1	2	.62
Obsessive-compulsive disorder	1	0	.50
Nicotine dependence	2	4	.67
Other	0	0	>.99

*Able to work only part-time or not at all.

†Baseline Wellness score data were available for 29 patients randomized to hydrocortisone and 35 to placebo.

‡Hamilton Depression Rating Scale data were available for 34 patients randomized to hydrocortisone and 34 to placebo.

§DSM-III-R indicates *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. The number of subjects with diagnosis is according to the computerized Diagnostic Interview Schedule.

them were taking systemic steroids. An additional 151 patients were excluded because they did not meet the 1988 CDC CFS case definition,² 109 eventually declined enrollment for unstated personal reasons, 61 had complicating medical conditions that precluded their study, 30 experienced onset of illness that was too gradual, 15 individuals did not meet the age criteria, 14 had contraindications to steroid use, and 2 were pregnant. In all, 74 patients were admitted for final

evaluation. Four proved too depressed to justify discontinuing their use of antidepressant medications.

Seventy patients were enrolled in the trial, 35 in each treatment arm. Their demographic and historical features, baseline self-rating scores, and adrenal-hormone status were well distributed between the 2 study arms. However, trends toward a shorter duration of illness, higher mean scores on the Beck Depression Inventory²⁶ and the Profile

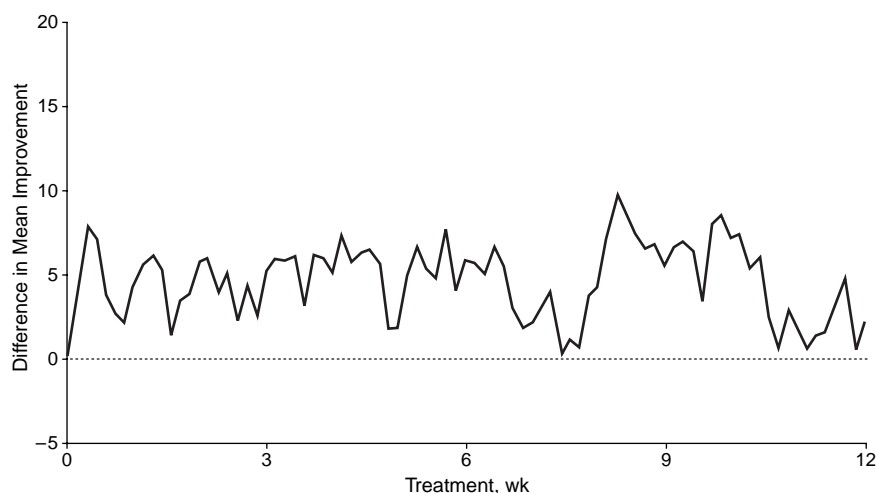


Figure 2.—A daily plot for the 12 weeks of treatment of the difference between means for hydrocortisone and placebo recipients in the change of Wellness scores from the pretreatment mean. On every day of treatment, the Wellness scores increased more from their baseline for hydrocortisone recipients than they did for placebo recipients.

of Mood States depression score,²³ and more individuals with no current *DSM-III-R* diagnoses²² were noted in those randomized to hydrocortisone (Table 1).

The 70 patients began treatment between May 1992 and December 1995. Seven patients terminated treatment prematurely, after 3 to 75 days. Five (2 hydrocortisone, 3 placebo) of them terminated due to their perceived exacerbation of symptoms of CFS. One additional placebo recipient developed a rash, and 1 hydrocortisone recipient decided to pursue a different (nonstudy) medication after 3 days. Two women who became pregnant during treatment were considered to have completed the study after 55 and 67 days. The remaining 61 patients received 76 to 96 days of therapy.

Efficacy

The 2 groups did not differ significantly in the percentage of subjects who recorded improvement in mean Wellness scores while receiving treatment: 19 (54.3%) of 35 placebo recipients and 20 (66.7%) of 30 hydrocortisone recipients ($P = .31$). There was, however, evidence that hydrocortisone treatment led to some improvement in patient status. First, the percentages of patients recording improvement of at least 5, 10, or 15 points on the Wellness scale were greater for hydrocortisone than placebo recipients (5 points, 53% vs 29%, $P = .04$; 10 points, 33% vs 14%, $P = .07$; and 15 points, 20% vs 6%, $P = .08$). Second, a plot of the difference between the average amount of improvement in Wellness score for each day (daily score minus pretreatment mean) showed that the hydrocortisone recipients improved quickly

and sustained a greater increase in Wellness scores than the placebo recipients for every day of the 12 treatment weeks (Figure 2). Comparison of the numbers of days on which average improvement was greater for the 2 groups reflects the consistently higher average improvement for hydrocortisone ($P < .001$ by Sign test). The mean improvement on treatment in the hydrocortisone group was 6.3 points, being higher than the mean improvement of 1.7 points for the placebo recipients ($P = .06$; Table 2).

While there were higher rates of improvement (data not shown) and mean changes from the pretreatment scores on most of the other rating scales and subscales for the hydrocortisone recipients, none of these differences was statistically significant (Table 2).

Analysis of Other Self-rating Instruments

For disorders with largely subjective features like CFS, one must use self-rating instruments to quantify patient performance and change. Here, we included a series of self-rating instruments, most of which have been validated individually in multiple other populations.²²⁻²⁶ The amount of improvement in Wellness score, which is defined by a remarkably simple, single-item global health scale, was significantly correlated with improvement in many of the other more complex and well-characterized scales. The Spearman correlations were generally similar for all treated subjects combined and for subjects receiving either hydrocortisone or placebo alone (data not shown). The significant correlations were positive for scales for which, like the Wellness score, positive changes indicated improve-

ment, and negative otherwise. For example, changes in the Wellness score correlated negatively with changes in the Profile of Mood States Fatigue scale ($r = -0.56$, $P < .001$), Confusion scale ($r = -0.42$, $P < .001$), the Beck Depression Inventory ($r = -0.42$, $P < .001$), and the Sickness Impact Profile score ($r = -0.45$, $P < .001$) and positively with changes in the Activity scale ($r = 0.37$, $P = .003$) and the Profile of Mood States Vigor scale ($r = 0.53$, $P < .001$).

Adverse Effects

Patients maintained daily records of adverse reactions. Some of these reactions included symptoms inherent in CFS itself such as fatigue, depressed mood, and difficulty with concentration.²³ Others, such as weight gain and acne, are well-recognized reactions to high doses of corticosteroids.²⁸ Table 3 shows that of 21 adverse reactions elicited, 3 occurred significantly more frequently in hydrocortisone recipients: increased appetite, weight gain, and difficulty in sleeping. Actual patient weights confirmed their reports. The mean (SD) weight gain among hydrocortisone recipients during treatment was 1.5 (1.9) kg, while that of the placebo recipients was 0.5 (1.9) kg, a small but statistically significant ($P = .02$) difference.

Endocrine Studies

The morning basal and cosyntropin-stimulated cortisol levels at entry were well matched between the study arms (Table 1). There was no significant correlation between the pretreatment basal or stimulated cortisol levels, or the mean change in level on stimulation, with any of the self-rating scores or their changes with treatment. For example, the Spearman rank correlation coefficients for changes in Wellness score with hydrocortisone treatment were 0.05 for both baseline serum cortisol levels ($P = .81$) and baseline stimulated cortisol responses ($P = .79$). The patients with the lowest cortisol levels and adrenal reserve were not the most symptomatic, nor were they more likely to respond to hydrocortisone treatment.

The placebo recipients showed no obvious changes in their basal and stimulated cortisol levels during the treatment period. The patients who received hydrocortisone, however, experienced significant adrenal suppression. Specifically, mean (SD) basal morning serum cortisol levels at the completion of the study (408 [152] vs 279 [179] nmol/L [14.8 [5.5] vs 10.1 [6.5] µg/dL for placebo and hydrocortisone recipients, respectively; $P = .002$) and the mean level achieved in response to cosyntropin (869 [102] vs 577 [248] nmol/L; $P < .001$ [31.5 (3.7) vs 20.9

Table 2.—Mean Changes in Self-rating Scores From the Pretreatment to Treatment Period in Hydrocortisone and Placebo Recipients*

	Hydrocortisone (n)	Placebo (n)	Hydrocortisone Mean – Placebo Mean	P Value†
Wellness scale‡	6.3 (11.7) [30]	1.7 (8.8) [35]	4.6	.06
Beck Depression Inventory	–2.1 (5.1) [34]	–0.4 (4.1) [34]	–1.7	.17
Activity scale‡	0.3 (1.1) [34]	0.7 (1.4) [34]	–0.4	.32
Sickness Impact Profile	–2.5 (6.4) [33]	–2.2 (6.8) [34]	–0.3	.85
Profile of Mood States questionnaire				
Anger	–1.6 (3.9) [34]	–0.8 (3.8) [34]	–0.8	.65
Anxiety	–0.8 (2.5) [34]	–2.1 (3.6) [34]	1.3	.08
Confusion	–1.1 (3.3) [34]	–1.4 (2.9) [34]	0.3	.83
Depression	–1.6 (4.6) [34]	0.0 (3.8) [34]	–1.6	.18
Fatigue	–3.6 (5.3) [34]	–1.8 (4.5) [34]	–1.9	.21
Vigor‡	1.2 (3.3) [34]	0.7 (3.3) [34]	0.5	.45
Symptom Checklist–90-R				
General severity index	–0.1 (0.2) [34]	–0.1 (0.2) [34]	0.0	.20
Positive symptom distress index	0.0 (0.3) [34]	–0.1 (0.3) [34]	0.1	.28
Positive symptom total	–2.6 (10.8) [34]	–2.4 (11.5) [34]	–0.2	.68
Hamilton Depression Rating Scale	–0.8 (3.8) [32]	0.1 (2.9) [33]	–0.8	.25

*Values in the hydrocortisone and placebo columns are mean (SD) scores. In calculating the difference between mean changes and P value for the Wellness scale, changes were estimated for 1 additional hydrocortisone recipient and 1 placebo recipient (see “Methods”).

†Value calculated from 2-sided Wilcoxon rank sum test with continuity correction.

‡Improvement in these scales is indicated by a positive change. For the other scales, improvement is reflected by a negative change.

(9.0) µg/dL) were reduced by steroid treatment. During posttreatment testing, 5 patients had depressed cortisol responses to cosyntropin (<276 nmol/L [<10 µg/dL]) and began on a tapering regimen of open hydrocortisone. Upon unblinding the study, all 5 were found to have been randomized to the steroid treatment arm. In addition, 7 patients had suboptimal posttreatment responses to cosyntropin (stimulated cortisol levels of 276–497 nmol/L [10–18 µg/dL]) and all 7 had been receiving hydrocortisone treatment.

COMMENT

In a randomized, double-blind, placebo-controlled trial in CFS, low-dose hydrocortisone treatment was associated with improvement in symptoms as measured by change in Wellness scores. This is the first such study, to our knowledge, to demonstrate improvement with a drug treatment of CFS.

Significant therapeutic benefit, however, was not evident by changes in other self-rating scales. More important, what little improvement might be attributable to hydrocortisone treatment was achieved at the expense of significant adrenal suppression. Twelve of 33 patients randomized to hydrocortisone, but none of 33 placebo recipients, showed suboptimal responses to cosyntropin challenge at the end of treatment ($P<.001$ by 2-sided Fisher exact test). Although steps were taken to avert serious or potentially life-threatening adrenal insufficiency in the face of emergent stress, the fact that it could happen with less cautious widespread use precludes the pres-

ent regimen of hydrocortisone or comparable doses of other systemic corticosteroids as acceptable choices for the prolonged treatment of CFS.

Other conclusions can be drawn from the study as well. First, many placebo recipients demonstrated some improvement on the Wellness score, as chance alone might predict; however, the magnitude of that improvement was small. Patients with CFS simply do not improve much through an observation period of 3 months. In this regard, the present data define thresholds of spontaneous clinical change that will prove invaluable in projecting sample size and study design in further trials. Specifically, the percentages of placebo recipients exhibiting 5-, 10-, and 15-point improvements in Wellness scores were 29%, 14%, and 6%, respectively.

Second, many subjects who were referred for this study proved ineligible for enrollment. Nearly 25% (151/638) did not meet CDC case criteria for the diagnosis.² Clearly, there remains considerable variability in how the case criteria are applied in the community.⁷ Another major reason for nonenrollment was the patients' perceived need for other medications. It is always difficult to know how fastidious one should be in designing a therapeutic trial like this one. To allow concomitant medications might better approximate the setting in which a new treatment will be used in the community, but it will add confounding issues that could complicate interpretation of adverse reports and treatment outcome. Clearly, our decision to select subjects who withheld many other medications might

Table 3.—Adverse Reactions to Hydrocortisone or Placebo Treatment

Adverse Reaction	Hydrocortisone (n = 35)	Placebo (n = 35)	P Value
Any reaction	31	27	.17
Rash	6	4	.49
Loss of appetite	4	8	.20
Increased appetite	17	8	.02
Weight loss	0	3	.24
Weight gain	19	8	.006
Acne	6	7	.76
Headache	14	13	.80
Fever	7	8	.77
Chills	5	8	.36
Nausea	11	12	.80
Diarrhea	8	8	>.99
Restlessness	7	7	>.99
Difficulty sleeping	17	8	.02
Stomach pain	10	9	.79
Increased urination	4	5	>.99
Light-headedness	11	10	.80
Depression	6	8	.55
Irritability	10	11	.79
Anxiety	5	4	>.99
Confusion	9	7	.57
Other	14	12	.62

have excluded the sickest subjects. Nevertheless, the results of the present study should be applicable to the typical CFS patient population because the degree of disability and clinical characteristics of those enrolled (Table 1) so well emulates that of other published CFS cohorts.^{10,29–31} To improve the homogeneity of the patient sample, enrollment was restricted to patients whose fatigue arose relatively acutely. As it turned out, less than 5% of subjects screened reported onset of their illness over a period of longer than 6 weeks. Moreover, that no patients screened were excluded for using systemic corticosteroids precludes the possibility that study enrollment was biased toward those less likely to respond to hydrocortisone.

Third, the present data indicate that prolonged, low-dose daily glucocorticoid use has risks. There are, to our knowledge, no other placebo-controlled trials of prolonged daily hydrocortisone treatment involving doses as low as those used here (25–35 mg, equivalent to approximately 6 mg of prednisone). Low-dose glucocorticoid replacement, defined as 20 to 40 mg of hydrocortisone in divided daily doses, was felt to be safe, to cause no symptoms other than occasional gastric distress, and to benefit patients with chronic fatigue.³² We found that low-dose hydrocortisone treatment has mild side effects (Table 3) and affords minimal therapeutic benefit for CFS, but significantly suppresses adrenal responsiveness.

Fourth, the data bear importantly on the basic hypothesis under which this study was undertaken, namely that CFS symptoms are perpetuated through suboptimal activity of the HPA axis.¹⁵ That the basal and stimulated-cortisol levels did not correlate with illness severity in this study (data not shown), nor were

they predictive of clinical improvement or response to treatment, argue against the hypothesis. The fact that there was evidence of symptomatic benefit in hydrocortisone recipients, however, is concordant with this hypothesis, and yet the limited benefit indicates that mere supplementation of cortisol is not sufficient. It is possible that a more salutary effect would derive from a different low-dose regimen, or from specific supplementation of corticotropin-releasing hormone or pharmacologic augmentation of its release, were these latter options to become feasible.^{33,34}

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