Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial

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Summary
Background Reports of mild hypocortisolism in chronic fatigue syndrome led us to postulate that low-dose hydrocortisone therapy may be an effective treatment.

Methods In a randomised crossover trial, we screened 218 patients with chronic fatigue. 32 patients met our strict criteria for chronic fatigue syndrome without co-morbid psychiatric disorder. The eligible patients received consecutive treatment with low-dose hydrocortisone (5 mg or 10 mg daily) for 1 month and placebo for 1 month; the order of treatment was randomly assigned. Analysis was by intention to treat.

Findings None of the patients dropped out. Compared with the baseline self-reported fatigue scores (mean 25·1 points), the score fell by 7·2 points for patients on hydrocortisone and by 3·3 points for those on placebo (paired difference in mean scores 4·5 points [95% CI 1·2–7·7], p=0·009). In nine (28%) of the 32 patients on hydrocortisone, fatigue scores reached a predefined cut-off value similar to the normal population score, compared with three (9%) of the 32 on placebo (Fisher’s exact test p=0·05). The degree of disability was reduced with hydrocortisone treatment, but not with placebo. Insulin stress tests showed that endogenous adrenal function was not suppressed by hydrocortisone. Minor side-effects were reported by three patients after hydrocortisone treatment and by one patient after placebo.

Interpretation In some patients with chronic fatigue syndrome, low-dose hydrocortisone reduces fatigue levels in the short term. Treatment for a longer time and follow-up studies are needed to find out whether this effect could be clinically useful.

Lancet 1999; 353: 455–58

Introduction
Chronic fatigue syndrome affects up to 2·6% of people who attend primary care in the UK and is also encountered in many medical specialties. Patients with chronic fatigue syndrome have a poor outcome: only 3% of patients spontaneously recover at 18 months of follow-up.

About 50% of patients with chronic fatigue syndrome have co-morbid major depression. However, the results from placebo-controlled trials of antidepressants differ; some studies show moderate efficacy, whereas others do not. Controlled studies suggest that graded exercise therapy and cognitive behavioural therapy are effective treatments, but are relatively expensive and not widely available because of a shortage of adequately trained therapists. In addition, many patients are wary of the rationale behind these treatments. Alternative effective treatments for chronic fatigue syndrome are needed.

Studies of the hypothalamo-pituitary adrenal (HPA) axis in chronic fatigue syndrome show a mild hypocortisolism of central origin, in contrast to the hypercortisolism of major depression. Given the overlap between the symptoms of Addison’s disease and chronic fatigue syndrome, Demitrack and colleagues postulated that this hypocortisolism may be important in the mediation of central fatigue. There are suggestions that this underactivity of the HPA axis could result from factors that are secondary to the primary aetiology of chronic fatigue syndrome, such as sleep disturbance. Whatever the origin, one possibility is that low circulating cortisol could act as a biological factor that contributes to fatigue chronicity and interacts adversely with perpetuating cognitive and behavioural processes. Thus, a rise in cortisol concentrations might improve fatigue.

We set out to test the hypothesis that low-dose hydrocortisone therapy would improve fatigue in chronic fatigue syndrome using a randomised, double-blind, placebo-controlled, crossover design.

Methods
Patients
Between November, 1995, and February, 1997, we recruited patients in London and Cambridge from established clinics that specialise in chronic fatigue syndrome. The study was approved by both local ethical committees. We included patients who fulfilled both international consensus criteria for chronic fatigue syndrome. All patients underwent medical screening that included physical examination and relevant investigation, with a minimum of urine analysis, full blood count, measurement of urea, electrolytes, and erythrocyte sedimentation rate, and tests for thyroid and liver function. Patients also had a baseline endocrine assessment that included an insulin stress test, a corticotrophin-releasing hormone test, and measurements of urinary free cortisol and adrenal antibodies (including 21-hydroxylase, measured by immunoprecipitation assay [RSR Ltd, Cardiff, UK]). A semistructured psychiatric examination was done by trained psychiatrists (AJC, GM, EH) to assess chronic

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218 patients screened

39 eligible

4 not randomised
1 depressed
1 moved away
2 withdrew consent

35 randomised

1 dropped out before receiving medication
2 removed from trial because of protocol violation

16 hydrocortisone for 1 month
16 placebo for 1 month

16 hydrocortisone for 1 month
16 placebo for 1 month

32 completed hydrocortisone treatment
32 completed placebo treatment

Figure 1: Trial profile

fatigue syndrome and exclude additional psychiatric disorders to prevent confounding effects. All participants gave their written informed consent to take part.

The exclusion criteria were: any co-morbid psychiatric disorder classified according to Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria; significant abnormalities on screening investigations; frank hypocortisolism on endocrine assessment; illness of longer than 100 months’ duration; use of prescribed medication in the 2 months before study entry; a medical contraindication for hydrocortisone; and an inability to attend hospital for screening tests or follow-up visits. Adrenal autoantibodies were negative in all patients.

Treatment
Randomisation was by means of a balanced design in blocks of four. Each patient was randomly assigned hydrocortisone first or placebo first for 28 days before they were crossed over to receive the other treatment. Randomisation was done by the clinical trial’s pharmacist who kept the codes until completion of the study. None of the staff or patients had access to the randomisation codes during the study. The first 16 patients were allocated 5 mg hydrocortisone, and the remainder received 10 mg. Drug preparations were in identical opaque white capsules. Patients were told to take one tablet each morning with breakfast for 28 days. The medication was dispensed by the investigator at each visit; compliance was assessed by counting returned tablets and by questioning patients.

Assessments
Patients were assessed at baseline and on day 28 of each treatment period. For all assessments, we were unaware of treatment allocation. In addition, women were assessed on day 1–7 of their menstrual cycle during each treatment period. For each assessment, participants attended our clinic at 0900 h with a 24 h urine collection that they had started to collect the previous day. Patients were assessed clinically and completed a series of questionnaires, before they underwent a standard insulin stress test with 0.15 U/kg bodyweight insulin. The primary outcome measures were: score on an 11-item self-administered fatigue scale, scored according to a likert 0, 1, 2, 3 system to be sensitive to change, and the clinician-administered clinical global impression scale. Secondary self-administered outcome measures were used to assess degree of disability (work and social adjustment scale [WSAS] and medical outcomes study short form 36 with physical function and role limitations subscales) and psychological symptoms (general health questionnaire). We defined full treatment response as a score on the fatigue scale at or below the median population score of 12. We also defined a reduction in score on the fatigue scale score from baseline of 9 or more as clinically significant; we chose this score to equate with the 30% fall in fatigue scores produced by the standard course of cognitive behavioural therapy. We incorporated the clinicians’ assessments by calculating the number of patients who had a “very much improved” or “much improved” score on the clinical global impression scale. The 24 h urinary free cortisol and the insulin stress test were used to assess HPA axis function. We used the symptom checklist of 40 items and the patient’s self-report to assess side-effects.

Statistical analysis
We calculated sample size according to previous published data on the fatigue scale in chronic fatigue syndrome. We estimated that a clinically significant drop in fatigue of 30% was equivalent to a reduction of 9 points on the fatigue scale. With a power of 80% and significant p value of less than 0.05, we calculated that 35 patients on both placebo and hydrocortisone would be needed to show at least a 4 point difference between the two treatments.

In the analysis, patients’ self-ratings were calculated as a change in scores from baseline after active treatment and after placebo. We then compared the two scores by paired t tests. We assessed the possibility of a carryover effect in patients on hydrocortisone as their first treatment by a comparison with patients on placebo first by means of independent t tests. We used the same method to assess any differential effect of the two doses of hydrocortisone. In addition, we compared the number of responders to active treatment or placebo by one-tailed Fisher’s exact test. Finally, we looked at the effect of hydrocortisone on the HPA axis compared with placebo by paired t tests. All patients were assessed by the clinical global impression scale at all time points; four patients had missing self-assessment data for some time points.

Results
The trial profile shows the numbers of patients throughout the trial (figure 1). None of the 32 valid patients who started treatment dropped out. Thus, our analysis is both on an intention to treat and treatment completers basis. Our compliance assessment suggested that no patient missed more than two doses of trial medication. The mean age of the 32 patients was 35.3 (range 19–58) years and 20 were women. Nine (28%) patients had a history of psychiatric illness, whereas 19 (59%) related the onset of their illness to an infection. The mean length of illness was 36 (28–45) months, and mean baseline fatigue score was 25.1 (23.7–26.5) points.

The two doses of hydrocortisone had no differential effect on fatigue scores. The mean fall from baseline in patients taking 5 mg or 10 mg hydrocortisone was 6.7 points and 7.5 points, respectively (95% CI for difference −7.4 to 5.7, p=0.9). The groups were therefore analysed together.

Compared with baseline, fatigue scores fell by a mean of 7.2 (4.0–10.3) points in the hydrocortisone group and by 3.3 (1.3–5.3) points in the placebo group. The paired comparison of hydrocortisone versus placebo yielded
A mean benefit in favour of active treatment of 4·5 (1·2–7·8) points (p=0·009). The results were not affected by which treatment was received first (figure 2). The mean effect size of hydrocortisone was 6·7 points in month 1 and 7·6 in month 2 (95% CI for difference –7·4 to 5·5, p=0·77) and that for placebo was 2·4 in month 1 and 4·5 in month 2 (–1·9 to 6·1, p=0·28).

Nine (28%) of the 32 patients responded fully to active treatment, whereas three (9%) responded to placebo (Fisher’s exact test, p=0·05). There was a clinically significant fall in fatigue in 11 (34%) patients after hydrocortisone treatment and in four (13%) after placebo treatment (p=0·04). According to the clinicians’ assessments with the clinical global impression scale, seven (21%) patients on hydrocortisone and two (6%) on placebo improved (p=0·07).

The mean disability scores on the WSAS improved with hydrocortisone but not with placebo. Furthermore, patients who responded fully to hydrocortisone had even greater falls in disability scores (table). Assessment of physical role limitations with the medical outcomes study short form 36 showed no significant improvement overall, but substantial improvement in patients whose fatigue responded to hydrocortisone compared with those who did not respond to hydrocortisone (p=0·06).

Before treatment, there were no differences between responders and non-responders in terms of severity of fatigue, disability, or endocrine measures. However, on the general health questionnaire responders had lower pretreatment scores than non-responders (12·4 vs 18·5 [95% CI for difference 16·7 to 88·2], p=0·006). The mean number of self-reported somatic symptoms fell slightly from 16·9 to 14·3 after hydrocortisone treatment (p=0·04), whereas placebo had no such effect (17·2 to 15·6, p=0·21). Side-effects were reported by three patients on hydrocortisone (exacerbation of acne, nervousness, and improvement in eczema) and by one patient on placebo (episode of fainting).

**Discussion**

This study shows that low-dose hydrocortisone results in significant reductions in self-rated fatigue and disability in patients with chronic fatigue syndrome. Moreover, about a third of patients had a clinically significant reduction in fatigue, most to a level at or below that of the general population, with accompanying reductions in disability.

The effect of low-dose hydrocortisone was to increase the overall 24 h cortisol output after 28 days of treatment. When taken together with the results of the insulin stress test, this increase suggests that the treatment strategy was successful, and led to a rise in circulating cortisol concentrations without significant compensatory suppression of endogenous cortisol production. From these preliminary data, there was no evidence of a dose-response effect, which if replicated would suggest that 5 mg is a sufficient dose of hydrocortisone. The dose of hydrocortisone required to simulate the normal production of endogenous cortisol varies between 20 and 30 mg. Both the 5 mg or 10 mg dose would therefore be consistent with replacement of the reported reduction in cortisol output of between 30–40% in patients with chronic fatigue syndrome. However, responses to hydrocortisone were not predicted by the degree of pretreatment endocrine disturbance: both response to insulin stress test and urinary free cortisol output were the same in subsequent hydrocortisone responders as non-responders. That the patients who responded to hydrocortisone had lower scores on the general health questionnaire is consistent with previous reports which suggest that psychiatric co-morbidity is a poor prognostic factor in chronic fatigue syndrome, although none of our patients had a formal psychiatric diagnosis.

In their controlled study of hydrocortisone in chronic fatigue syndrome, McKenzie and colleagues used 25–35 mg doses of hydrocortisone and found a slight therapeutic effect on some measures and evidence of substantial adrenal suppression. They concluded that the risks of hydrocortisone outweighed the benefits at this high dose, but did not rule out potential benefits from different low-dose regimens.

The clinical relevance of the effects of hydrocortisone is not known. Most of our patients did not enter the trial, because of psychiatric co-morbidity or concomitant medication. The effects of hydrocortisone on disability are less than those seen after cognitive behavioural therapy, although this greater improvement takes up to 12 months. With cognitive behavioural therapy, fatigue is

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**Table: Fatigue score change from baseline**

<table>
<thead>
<tr>
<th>Work and social adjustment scale</th>
<th>Baseline</th>
<th>Placebo (n=32)</th>
<th>Hydrocortisone (n=32)</th>
<th>Responders (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home activities</td>
<td>4·8</td>
<td>–0·04</td>
<td>–2·1†</td>
<td>–2·1†</td>
</tr>
<tr>
<td>Private leisure activities</td>
<td>4·9</td>
<td>–0·66</td>
<td>–1·0†★</td>
<td>–2·6†★</td>
</tr>
<tr>
<td>Social leisure activities</td>
<td>5·8</td>
<td>–0·3</td>
<td>–1·1†★</td>
<td>–2·3†★</td>
</tr>
<tr>
<td>Relationships</td>
<td>5·7</td>
<td>–0·8</td>
<td>–0·5</td>
<td>–1·4†</td>
</tr>
<tr>
<td>Work</td>
<td>6·1</td>
<td>–0·2</td>
<td>–0·8†</td>
<td>–1·7†★</td>
</tr>
<tr>
<td>Mean score</td>
<td>5·1</td>
<td>–0·05</td>
<td>–0·7†</td>
<td>–2·0†★</td>
</tr>
</tbody>
</table>

All changes are from baseline, p<0·05 for all comparisons (hydrocortisone vs baseline, hydrocortisone vs placebo, hydrocortisone responders vs non-responders).

* Score of 0=no disability, 5=maximum disability. t=treatment vs placebo, n=number of patients. £p<0·05 vs treatment, $p<0·05 vs baseline. §p<0·05 vs non-responders to hydrocortisone.

Disability scores

The mean value after hydrocortisone was 141 (100–181) nmol per 24 h and was 97 (76–119) nmol per 24 h after placebo (95% CI for difference 14 to 74, p=0·006). There was no difference in the urinary free cortisol between the two doses of hydrocortisone (–118 to 45 nmol per 24 h, p=0·36). The maximum serum cortisol reached during insulin stress test was 898 nmol/L after placebo and 864 nmol/L after hydrocortisone (95% CI for difference –141 to 75, p=0·52).

The mean number of self-reported somatic symptoms fell slightly from 16·9 to 14·3 after hydrocortisone treatment (p=0·04), whereas placebo had no such effect (17·2 to 15·6, p=0·21). Side-effects were reported by three patients on hydrocortisone (exacerbation of acne, nervousness, and improvement in eczema) and by one patient on placebo (episode of fainting).
reduced less dramatically than disability, which suggests that such therapy is effective at changing the behavioural and cognitive factors that contribute to the generation and perpetuation of avoidance, disability, and sleep disturbance, but that subjective fatigue may be related to factors modified more indirectly by therapy. This explanation would be consistent with our suggestion that fatigue is perpetuated, at least in some patients, by low concentrations of cortisol. Further evidence of the link between low cortisol concentrations and fatigue comes from patients with frank glucocorticoid insufficiency in whom fatigue is a prominent complaint. Furthermore, in the overtraining syndrome, which has many similarities to chronic fatigue syndrome, prospective studies showed the development of fatigue is paralleled by a reduction in cortisol concentration.

The side-effects and long-term effects of corticosteroid treatment are well known, though these usually relate to substantially higher doses than those used in this study. Although it is possible that the antifatigue effect is not specific, in that steroids can cause mood changes such as increased energy in various conditions, again this effect usually occurs with much higher immunosuppressive doses. We also do not know whether any treatment effects persist; indeed, we found a rapid attenuation of therapeutic effect when patients were switched to placebo. Further studies are needed to investigate longer durations of treatment, the effect of treatment in combination with self-help or therapist-guided cognitive behavioural therapy, and the long-term outcome after treatment discontinuation. Until this research is concluded, we suggest that our trial may help to increase our understanding of the possible role of hypocortisolism in the pathogenesis of symptoms in chronic fatigue syndrome, and we would not recommend the widespread use of hydrocortisone as a treatment strategy.

Contributors
Anthony Cleare contributed to study design, recruitment, screening, testing, and monitoring of patients, and statistical analysis. Emma Heap contributed to the recruitment, screening, testing, and monitoring of patients. Anthony Cleare wrote the manuscript and all investigators contributed critical revisions for the final version.

Acknowledgments
Angela Barry, clinical trials pharmacist at King’s Healthcare, London, prepared the drugs and randomisation protocol. Laura Young, endocrine nurse, and Samantha Sookdeo, research technician, helped with endocrine tests and data entry. Roy Sherwood and Jenny Jones assisted with hormone assays in urine and blood. We thank Matthew Hotopf for statistical advice. The Linbury Trust provided a project grant in support of this study, and Anthony Cleare is supported by a Linbury Trust Senior Research Fellowship.

References