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The prednisolone suppression test in depression: Dose—response and changes with antidepressant treatment

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Summary

Depressed patients have reduced glucocorticoid receptor (GR) function, as demonstrated by resistance to the suppressive effects of the synthetic glucocorticoid hormone, and GR agonist, dexamethasone. We have developed a suppressive test with prednisolone, a synthetic glucocorticoid that is similar to cortisol in its pharmacodynamics and pharmacokinetics, and binds to both the GR and the mineralocorticoid receptor (MR). We have found that depressed patients suppress normally to prednisolone, unless they are particularly non-responsive to treatment. In the present study, we evaluated 28 inpatients with treatment-resistant depression (TRD), and compared salivary cortisol secretion (at 0900 h, 1200 h and 1700 h) after placebo or after prednisolone (5 mg), before and after an inpatient treatment admission. Half of the patients ($n = 14$) reached treatment response. When comparing the assessment between admission and discharge, cortisol output after placebo fell (–26% of area under the curve; $p = 0.024$) while the output after prednisolone did not change. Moreover, there was no change in the response to prednisolone (percentage suppression) between admission at discharge, and this was not influenced by treatment response. Finally, we could confirm and extend our previously published data with prednisolone (5 mg), showing that depressed patients ($n = 12$) and controls ($n = 12$) suppressed equally to both 5 and 10 mg doses of prednisolone. This study suggests that the response to prednisolone is similar in depressed patients and controls at different doses of prednisolone, and does not change with symptomatic improvement. This is in contrast with findings, from us and others, using other measures of hypothalamic—pituitary—adrenal axis

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Conflict of interest

None of the authors have any interest to declare.

function, such as basal cortisol levels or the response to dexamethasone. Thus, we propose that the prednisolone suppression test may offer specific biological and clinical information, related to its action at both the GR and the MR.

Keywords

Cortisol; Depression; Glucocorticoid receptor; Hypothalamic—pituitary—adrenal (HPA) axis; Mineralocorticoid receptor; Prednisolone; Negative feedback; Treatment-resistant depression

1. Introduction

We have recently developed a novel suppressive test for the hypothalamic—pituitary—adrenal (HPA) axis, using the synthetic glucocorticoid prednisolone (Pariante et al., 2002, 2004; Juruena et al., 2006, 2009b). Compared to dexamethasone, used in the more traditional dexamethasone suppression test (DST) and dexamethasone/corticotrophin releasing hormone (DEX/CRH) test, prednisolone mimics more closely the pharmacological profile of the endogenous glucocorticoid, cortisol. In fact, whilst dexamethasone only probes the function of the “low-affinity” cortisol receptor (glucocorticoid receptor, or GR), prednisolone probes both GR and the “high-affinity” cortisol receptor (mineralocorticoid receptor, or MR). Furthermore, the half-life of prednisolone is also similar to that of cortisol, while dexamethasone has a 2—4-fold longer half-life (Orth and Kovacs, 1998). Therefore, the prednisolone test has been proposed as a more naturalistic test for the HPA axis to be used in biological psychiatry (Pariante et al., 2002, 2004; Juruena et al., 2006, 2009b).

Our research in depressed inpatients has indeed shown that the HPA axis response to prednisolone is different from the response to dexamethasone: that is, depressed patients tend to show impaired HPA axis suppression by dexamethasone, indicating impaired GR function, but normal HPA axis suppression by prednisolone (Juruena et al., 2006). We have interpreted these findings as suggesting an intact or even increased MR function, compensating for the impaired GR. Indeed, these results and their interpretation are consistent with a study by Young et al., who assessed MR function using an MR antagonist, spironolactone (Young et al., 2003), and also found intact response in depressed patients.

Interestingly, the DEX/CRH test is considered a “state” marker in depression, with studies showing normalization of the cortisol response to DEX/CRH challenge after successful antidepressant treatment (Ising et al., 2007). We have recently shown that, although the response to prednisolone is overall normal in depressed patients, a subgroup of patients who will later fail to respond to an inpatient therapeutic package does show impaired response to prednisolone (Juruena et al., 2009b). In the present study, we describe the prospective changes in the prednisolone suppression test before and after receiving the intensive inpatient therapeutic package, and their relationship with the clinical improvement.

Finally, our studies have been conducted using a “low” dose (5 mg) of prednisolone, leading to approximately 40% suppression of cortisol production in normal individuals the following day; in contrast, dexamethasone 0.5 mg, for example, leads to approximately 85% suppression of cortisol production in normal individuals the following day (Pariante et al., 2002; Juruena et al., 2006). In the present study, we also describe the effects of two different doses of prednisolone (5 and 10 mg) in depressed patients and matched controls.

2. Methods

The study utilized a single-blind, non-randomized, placebo-controlled, repeated measure design, as previously described (Pariante et al., 2002, 2004; Juruena et al., 2006, 2009b). Briefly, on Day 1, 28 depressed inpatients received placebo capsules, and on Day 2 they received 5 mg prednisolone capsules, both at 2200 h. No alcohol, coffee, tea or meals were allowed after each capsule. On the day following each capsule administration, saliva samples were collected at 900 h, 1200 h and 1700 h. The test was administered shortly after admission (range 5–21 days), and then repeated before discharge, after an median of 21 weeks of inpatient stay (range 6–57 weeks).

Twelve depressed subjects also received 10 mg of prednisolone on Day 3, at least 48 h after Day 2, again at 2200 h. Twelve healthy controls also received prednisolone 10 mg. Subjects were then assessed as above.

Patients in this study belong to a larger sample ($n = 45$) who completed the test at baseline, as recently described (Juruena et al., 2009b), and were all inpatients on the National Affective Disorders Unit (ADU) of the Bethlem Royal Hospital (South London and Maudsley NHS Trust). Both the clinical assessment and the therapeutic intervention have been extensively described before (Fekadu et al., 2009; Juruena et al., 2009b). Briefly, they were all diagnosed as having unipolar major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition — DSM-IV (American Psychiatric Association, 1994), using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 1997). In addition, all patients were treatment resistant on the basis of prior non-response to at least two different classes of antidepressants, as assessed by the Antidepressant Treatment History Form (Sackeim et al., 1990). The degree of treatment resistance was staged according to the criteria of Thase and Rush (1997). For clinical severity of depression, we used the 21-item Hamilton Rating Scale for Depression (HAMD-21) (Hamilton, 1960). The therapeutic intervention consisted of an individualised combination of the following therapies as clinically indicated for each patient: (1) intensive psychopharmacology utilising combinations of medications as guided by the Maudsley Prescribing Guidelines (Taylor et al., 2005); (2) weekly cognitive behavioural therapy; (3) daily occupational therapy; (4) fortnightly couple therapy; (5) alleviation of any physical health consequences or corollaries of depression (such as hypercholesterolaemia, hypertension, obesity, malnutrition and dental problems); and (6) supportive and enabling nursing care including group sessions for anxiety management and behavioural activation (Juruena et al., 2010). Patients' response to treatment was carefully assessed by repeating shortly before discharge the same psychometric measures that were administered at baseline. Response was defined as a reduction of HAMD-21 score of 50% or greater, while remission was defined as reduction HAMD-21 score to 7 or below. Exclusion criteria for the study were: a history of hypersensitivity to corticosteroids or steroid use; heavy smokers (more than 25 cigarettes/day); viral illnesses during the preceding 2 weeks; pregnant or lactating women; alcohol dependence; and significant physical illnesses (for example, severe allergies, autoimmune diseases, hypertension, malignancy, haematological, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurological disease). Patients with bipolar affective disorder, psychotic symptoms unrelated to their depressive disorder, or an organic aetiology were excluded. The study protocols were all approved by the Research Ethical Committee of the Institute of Psychiatry and South London and Maudsley NHS Trust. Written informed consent was obtained from all subjects. Healthy controls were recruited from hospital staff, students and the local community. The 12 patients and 12 controls who received prednisolone 10 mg were matched according to age (to within a limit of 5 years), gender and body mass index (BMI; within a range of $\pm 5\text{kg/m}^2$).

The protocol for the salivary collection has been described before (Pariante et al., 2002, 2004; Juruena et al., 2006, 2009b). Both patients and controls were admitted to the research rooms of the ADU, where they spent the period 0845–1715 h engaged in sedentary activities. Snacks, meals and drinks were standardized throughout the day. Saliva samples were collected using Salivettes (Sarstedt, Leicester, UK), and cortisol concentrations measured using a time-resolved immunofluorescent assay (TR-FIA), as previously described (Juruena et al., 2009b, 2010).

Plasma levels of prednisolone (from samples collected at 9:00 the following morning) were measured by high performance liquid chromatography (Hewlett-Packard UV Detector linked to Chemstation collection system), again as previously described (Juruena et al., 2009b).

The general linear model (GLM) analysis for repeated measures was used to examine within-group differences (admission vs. discharge) in cortisol levels after placebo and prednisolone. As previously described, we also used as summary measures the total salivary cortisol output, calculated as the area under the curve (AUC) using the trapezoidal method, after placebo and prednisolone, and further calculated the percentage suppression of salivary cortisol for each individual. The latter is a measure of suppression that is independent of the absolute cortisol levels (Pariante et al., 2002, 2004; Juruena et al., 2006, 2009b, 2010). We used *t* tests (paired, when appropriate) to compare clinical data, AUC values, percentage suppression, and prednisolone plasma levels, between admission and discharge, or patients and controls (for the 10 mg only). All values are presented as means (and \pm standard error of the mean [SEM]).

3. Results

The sample included 21 females (75%), and had a mean age of 51.5 (\pm 10.3) years. Twenty-three were taking medication, while five (18%) were drug free for at least 14 days before placebo and prednisolone challenge. All the remaining were receiving either a selective serotonin reuptake inhibitor or a serotonin and noradrenaline (non-tricyclic) reuptake inhibitor, often in combination with a mood stabilizer ($n = 20$). Further clinical details are described in Table 1.

The HAMD-21 mean scores were 25.2 (\pm 1.0) at admission and 16.5 (\pm 1.5) at discharge. Although the overall decrease in HAMD-21 was significant ($t = 5.3$, $df = 27$, $p < 0.001$), only half of the patients ($n = 14$) reached treatment response, and a quarter ($n = 7$) reached remission. This was not unexpected, as they all qualified as a previously treatment-resistant population.

The cortisol levels after placebo and the prednisolone suppression test were conducted at the beginning of the inpatient treatment, and shortly before discharge. The GLM analysis tested the differences between admission and discharge, separately for placebo and prednisolone, using the individual cortisol levels measured at 900 h, 1200 h and 1700 h (see Fig. 1).

The results show that cortisol levels output after placebo, but *not* after prednisolone, changed significantly between admission and discharge. Cortisol levels after placebo decreased between admission and discharge by approximately 26% of cortisol output ($F = 5.4$, $df = 1, 54$; $p = 0.024$). However, there was no difference in cortisol levels output after prednisolone between admission and discharge ($F = 1.3$, $df = 1, 54$; $p = 0.3$).

More importantly, when we tested the ability of prednisolone to suppress the HPA axis at admission and discharge, using the percentage suppression, we found no changes in the sensitivity to prednisolone. Indeed, there was a small and not significant *reduction* in the

percentage suppression (that is, patients becoming less sensitive): -35.4% (± 6.7) at admission vs. -27.1% (± 6.8) at discharge ($t = -1.1$; $df = 27$; $p = 0.3$).

Interestingly, the change in percentage suppression was not influenced by treatment response, as shown in Fig. 2. We have previously described (in a larger sample, including the patients presented here) that the suppressive response to prednisolone is impaired in patients who subsequently fail to respond to our inpatient therapeutic package (Jurueña et al., 2009b). Also in this subsample we found that the response to prednisolone at admission was impaired in subsequent nonresponders vs. responders (approximately -27% vs. -44%). However, this response did not change between admission and discharge, in either of the two groups: approximately -27% at admission vs. -21% at discharge in non-responders ($t = -0.8$; $df = 13$; $p = 0.45$) and -44% at admission vs. -33.5% at discharge in responders ($t = -0.8$; $df = 13$; $p = 0.4$) (see Fig. 2). Also, there were no changes in prednisolone plasma levels between admission and discharge: 34.1 (± 5.8) ng/ml at admission vs. 29.1 (± 5.6) ng/ml at discharge ($t = 0.6$; $df = 27$; $p = 0.5$).

Finally, the dose—response study shows that depressed patients and controls suppressed equally to both the low and the high doses of prednisolone, as shown in Fig. 3. The percentage suppression was approximately vs. -40% in patients -50% in controls after 5 mg ($t = -1.1$; $df = 22$; $p = 0.3$), and -59% in patients vs. -69% in controls ($t = 0.9$; $df = 22$; $p = 0.4$) after 10 mg of prednisolone (see Fig. 3). As expected, prednisolone plasma levels were higher after the 10 mg than after the 5 mg dose, both in patients and controls: 66.5 (± 10.9) ng/ml after 5 mg vs. 85.5 (± 10.2) ng/ml after 10 mg in patients ($t = -2.8$; $df = 11$; $p = 0.02$), and 56.1 (± 5.1) ng/ml after 5 mg vs. 90.9 (± 10.1) ng/ml in controls ($t = -2.9$; $df = 11$; $p = 0.015$).

4. Discussion

We present here two separate but complementary studies bringing additional information on the prednisolone suppression test in patients with treatment-resistant depression. First, the response to prednisolone does not change before and after an inpatient therapeutic intervention, even in those who respond to treatment. Second, as we have previously demonstrated for the lower (5 mg) dose (Jurueña et al., 2006, 2009b), the higher (10 mg) dose of prednisolone also suppresses equally cortisol levels in patients and controls.

We have previously argued that the prednisolone suppression test, differently from the DST and the DEX/CRH test, probes both the MR and the GR (Jurueña et al., 2006, 2009b). Indeed, in a previous study comprising 18 of the 28 subjects of this study, we found that patients with major depression tend to have a normal response to prednisolone even in the presence of an impaired (GR-mediated) response to dexamethasone (Jurueña et al., 2006). Specifically, in the previous study we administered dexamethasone (0.5 mg), and found, as expected, an impaired suppression by dexamethasone: cortisol output during the day was decreased by 85% in controls but only by 46% in depressed patients (an effect size difference of $d = 1.6$). However, the same depressed patients showed normal suppression by prednisolone (5 mg): suppression was -41% in controls and -36% in depressed patients (Jurueña et al., 2006). This theoretical framework is consistent with studies assessing MR function and MR expression in depression and bipolar illness, that also found no difference between patients and controls (Lopez et al., 1998; Young et al., 2003; Jurueña et al., 2009a). Moreover, the current study confirms and extends our published findings, not only by replicating, in a new sample, similar suppression by prednisolone 5 mg in patients and controls, but also by showing similar suppression by prednisolone 10 mg.

We have also previously found that a subgroup of highly resistant depressed patients does show an impaired response to prednisolone, and this is indeed associated with a lack of future response to an inpatient treatment package (Juruena et al., 2009b, 2010). A subset of this sample is described here, and again we were able to show this difference (approximately 17%) which is almost identical to the difference in the larger published sample (approximately 21%). This paper extends these findings by demonstrating that the response to prednisolone is stable, and does not change with symptomatic improvement. Indeed, it might be considered surprising that the response to prednisolone changed little between admission and discharge, considering that this is an inpatient unit where the subjects received an intense clinical package, including optimisation of pharmacological treatment as well as psychotherapeutic intervention. This lack of change in the response is in contrast with the clear improvement in depressive symptoms that these subjects showed overall, and is not influenced by whether subjects did or did not respond to treatment at the time of their discharge. Of note is also that subjects did show changes in other aspects of the HPA axis (i.e., reduction in cortisol production during the day). Other studies have also shown that the response to the DEX/CRH test changes with symptomatic improvement (Ising et al., 2007). It is the response to prednisolone that seems to remain unchanged.

Based on our findings, we would speculate that MR function (as measured by the response to prednisolone) is a stable aspect of HPA axis activity, which does not change, in depressed subjects, with improvement in symptoms. Therefore, an abnormal MR function (as measured by an impaired response to prednisolone) could be considered a stable biomarker of poor clinical course and lack of response to treatment. Indeed, the notion that effective MR functioning is required for therapeutic response in depression is supported also by studies showing that MR blockade worsens depressive symptoms (Holsboer, 1999) and that MR stimulation improves response to treatment (Otte et al., 2010). Alternatively, the lack of changes in the response to prednisolone may be explained by the specific features of this clinical sample. First of all, being a treatment-resistant group, this sample had low rates of response (50%) and remission (25%). Improvement in the HPA axis response to DEX/CRH in previous studies is particularly evident in those who reach remission at discharge (Binder et al., 2009) and therefore our sample may simply not have improved enough to show relevant biological changes in HPA axis function. Moreover, patients with bipolar or psychotic depression show a lack of normalisation of the DEX/CRH test even in the presence of improvement in depressive symptoms (Owashi et al., 2008; Hennings et al., 2009; Juruena et al., 2009a); although bipolar patients were excluded from the study sample, this is a particularly severe treatment-resistant sample, and some patients had mood-congruent psychotic symptoms. Finally, normalisation of the HPA axis activity occurs as early as the first 1–2 weeks of antidepressant treatment, and some studies have shown that a longer duration of admission is associated with an increase, rather than a decrease, of HPA axis activity (Zobel et al., 1999). Since the average duration of admission in our subjects was 21 weeks, it is possible that patients exhibited a degree of this “late increase” before being retested. Indeed, this late increase in HPA response to DEX/CRH at discharge is a predictor of future (within the following 6 months) relapse (Zobel et al., 1999), and our clinical population is also at a high risk of relapsing and/or of remaining continuously ill (Fekadu et al., 2009).

In summary, and notwithstanding the clear limitation of the small sample size, this study is the first in which the prednisolone suppression test has been repeated after treatment, and adds to the mounting evidence that this novel challenge may probe different aspects of the HPA axis compared to the classic DST and DEX/CRH test.

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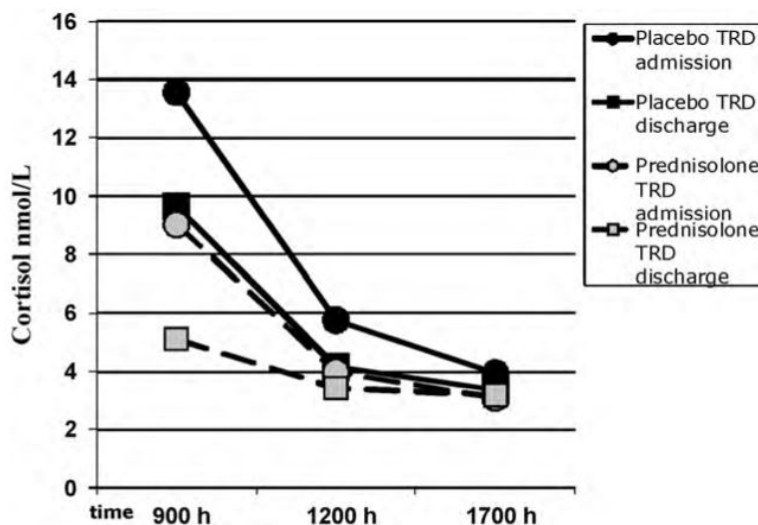


Figure 1. Cortisol output levels between 0900 h and 1700 h in a sample ($n = 28$) of depressed inpatients with treatment-resistant depression (TRD), at admission (circles) and discharge (squares), after placebo (continuous line) and prednisolone (5 mg; dashed line). A general linear model analysis for repeated measures was used to examine within-group differences (admission vs. discharge) in cortisol levels after placebo and prednisolone. Cortisol levels after placebo fall significantly between admission and discharge, but not cortisol levels after prednisolone.

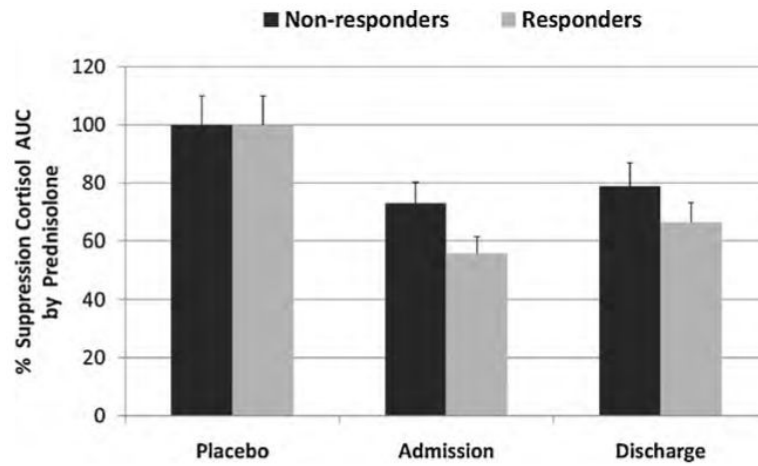


Figure 2. Cortisol output, measured as percentage area under the curve relative to placebo, in a sample of depressed inpatients ($n = 28$) after placebo and prednisolone (5 mg), at admission and discharge. The response to prednisolone did not change in either patients who subsequently responded to treatment ($n = 14$; in gray) or patients who did not respond ($n = 14$; in black).

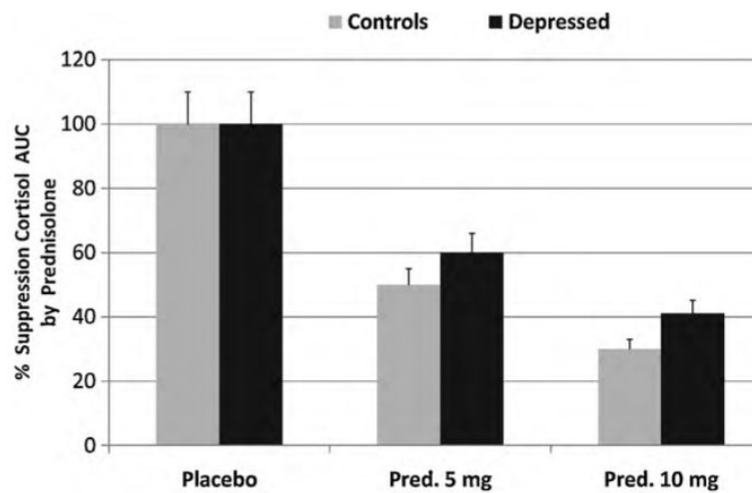


Figure 3. Cortisol output, measured as percentage area under the curve relative to placebo, in a sample of depressed inpatients ($n = 12$; black) and matched controls ($n = 12$, gray) after placebo, prednisolone (5 mg), and prednisolone (10 mg). The dose—response study shows that depressed patients and controls suppressed equally to both the low and the high doses of prednisolone.

Table 1

Demographics and clinical features of treatment-resistant depression patients (TRD), whole sample $n = 28$. Mean (SEM) or n (%)

	Treatment-resistant depression ($n = 28$)
Gender (%)	21 f (75%)
Age (y)	51.5 (2.0)
BMI (Kg/m ²)	29.3 (1.0)
Current medication (%)	SSRI/SNRI 23 (82%) Mood stabilizer 20 (71%) Other(s) clinical medications 17 (60%) Benzodiazepine 16 (57%) Atypical antipsychotic 11 (29%) Tricyclic antidepressant 7 (20%) MAOI 5 (18%) Drug free 5 (18%) Other antipsychotic 2 (07%)
ECT in the past (%)	22 (79%)
TRD stage: n (%)	Stage 5: 23 (82%) Stage 4: 01 (4%) Stage 3: 04 (14%)