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SHORT COMMUNICATION

DIAGNOSTIC PERFORMANCE OF THE THIRTY-FOUR HOUR DEXAMETHASONE SUPPRESSION TEST

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SUMMARY

The performance of the dexamethasone suppression test (DST) in the diagnostic confirmation of endogenous depression was compared according to two times of blood collection—1600 hr on day 2 (usual sample) and 0800 hr on day 3 (34 hr after dexamethasone intake)—in 14 endogenous depressives and in a control group of 17 psychiatric inpatients with other diagnoses. For the day 2 (1600 hr) sample, a 5 μg/dl cortisol concentration represented the best cut-off score, with sensitivity of 57% specificity of 88%, and diagnostic confidence of 80%. For the day 3 (0800 hr) sample, the best cut-off score was 20 μg/dl, with the same sensitivity (57%) but there was a decrease of both specificity (to 76%) and diagnostic confidence (to 67%). The mean cortisol levels were much higher on day 3 than on day 2, suggesting that the inhibitory activity of dexamethasone was no longer present.

INTRODUCTION

THE OVERNIGHT dexamethasone suppression test (DST) currently represents one of the most widely used biological markers of endogenous depression, both for in- and outpatients (Carroll, 1982). About 50% of endogenous depressives exhibit an abnormal cortisol 'escape' after dexamethasone; however, the specificity of this phenomenon in endogenous depression has been a subject of recent controversy (Hirschfeld *et al.*, 1983). The DST procedure has not been fully standardized to date. According to Carroll *et al.* (1981), oral intake of dexamethasone (1 mg) at 11 p.m. on day 1 is followed by measurement of plasma cortisol levels at 1600 hr and 2300 hr on day 2, and non-suppression is defined as a cortisol level higher than 5 μg/dl in either sample.

Goldberg (1980a,b) used a modification of the DST procedure as a potential indicator of safe withdrawal of antidepressant therapy, with measurement of plasma cortisol at 0900 hr on day 3 (34 hr after dexamethasone intake). However, other studies in normal subjects (Tourigny-Rivard *et al.*, 1981) and in major depressive patients (Faber, 1983) have suggested that cortisol levels at 0800 hr on day 3 do not differ significantly from baseline levels. Since a morning sample may be easier to obtain, especially in outpatients, we replicated the study of Faber (1983) by comparing the diagnostic performance of the DST based on cortisol measurements at 1600 hr on day 2 and at 0800 hr on day 3.

SUBJECTS AND METHODS

Subjects

The study was performed in 31 inpatients newly admitted to the Psychopharmacology Unit of the University Hospital of Liège, Belgium. All diagnoses were made according to the Research Diagnostic Criteria (RDC)

(Spitzer *et al.*, 1978) by two independent research psychiatrists using a semi-structured interview and blind to the laboratory results. The sample was composed of 14 primary major depressives, endogenous subtype (seven male and seven female), ages 27 to 66 years (mean age = 46.6 ± 13.7 years). The control group (11 male and six female), ages 23 to 58 years (mean age = 43 ± 10.7 years) included six secondary major depressives who did not meet RDC for endogenous subtype, six patients suffering from minor depression, two phobics, two manics and one schizophrenic. Patients presenting any medical illness, as evidenced by history, physical examination, EKG, EEG, chest X-ray and routine laboratory tests, were excluded. All patients were free of any medication for at least two weeks at the time of the DST and, prior to participation, gave informed consent.

DST procedure

Patients took dexamethasone (1 mg p.o.) at 2300 hr on day 1. Blood samples (10 cc) were collected at 1600 hr on day 2 and at 0800 hr on day 3. Cortisol was measured by radioimmunoassay (Sulon *et al.*, 1978). According to the standard cut-off limit, patients were defined as non-suppressors if the 1600 hr plasma cortisol level was above 5 μg/dl (Carroll *et al.*, 1981).

Data analysis

The cortisol levels were used to calculate the sensitivity, specificity, and diagnostic confidence of the DST, according to the definitions of Vecchio (1966), sensitivity referring to the proportion of endogenous depressives exhibiting DST non-suppression, specificity referring to the proportion of control patients exhibiting normal suppression, and diagnostic confidence referring to the proportion of non-suppressors who were endogenous depressives.

Paired *t*-tests (two-tailed) were used to analyze the within-patient cortisol differences between day 2 and day 3, and group *t*-tests (two-tailed) were used to analyze the differences between endogenous depressives and controls. Since plasma cortisol concentrations tend to be log-normally distributed, the data were also analysed using a natural log (ln) transformation. Since the results of both analyses were quite similar, only the non-transformed values are reported herein.

RESULTS

The distributions of cortisol levels at 1600 hr on day 2 and at 0800 hr on day 3 in the endogenous depressives and the control group are displayed in Fig. 1. At 1600 hr on day 2, the mean cortisol level for the entire sample was 6.0 ± 6.1 μg/dl. The endogenous depressives exhibited a significantly higher mean cortisol level than the control group (8.50 ± 6.79 μg/dl vs 3.94 ± 4.72 μg/dl, $T = 2.20$, $p < 0.05$). Using the standard cut-off limit (5 μg/dl), eight endogenous depressives were non-suppressors and six were suppressors. Among the control group, 15 patients exhibited normal suppression, and two were non-suppressors (both secondary depressives). These results correspond to a sensitivity of 57%, a specificity of 88%, and a diagnostic confidence of 80%. Other cortisol cut-off limits did not improve the diagnostic performance.

At 0800 hr on day 3, the mean cortisol level for the entire sample was clearly higher than on day 2 (17.36 ± 6.96 μg/dl vs 6.00 ± 6.10 μg/dl, $T = -6.8$, $p < 0.0001$), as it was for the endogenous depressives (19.89 ± 6.11 μg/dl vs 8.5 ± 6.8 μg/dl, $T = -4.67$, $p < 0.0002$) and the control group (15.28 ± 7.09 μg/dl vs 3.94 ± 4.72 μg/dl, $T = -5.49$, $p < 0.0001$) separately. There was no significant difference in cortisol level between the endogenous depressives and the control group (19.89 ± 6.1 μg/dl vs 15.28 ± 7.09 μg/dl, $T = 1.92$, $p =$ NS). The best cortisol cut-off was 20 μg/dl, which yielded a sensitivity of 57%, a specificity of 76%, and a diagnostic confidence of 67%.

DISCUSSION

Normal subjects respond to the overnight 1.0 mg DST with plasma cortisol suppression for at least 24–28 hr, as indicated by catheter studies and by less frequent blood

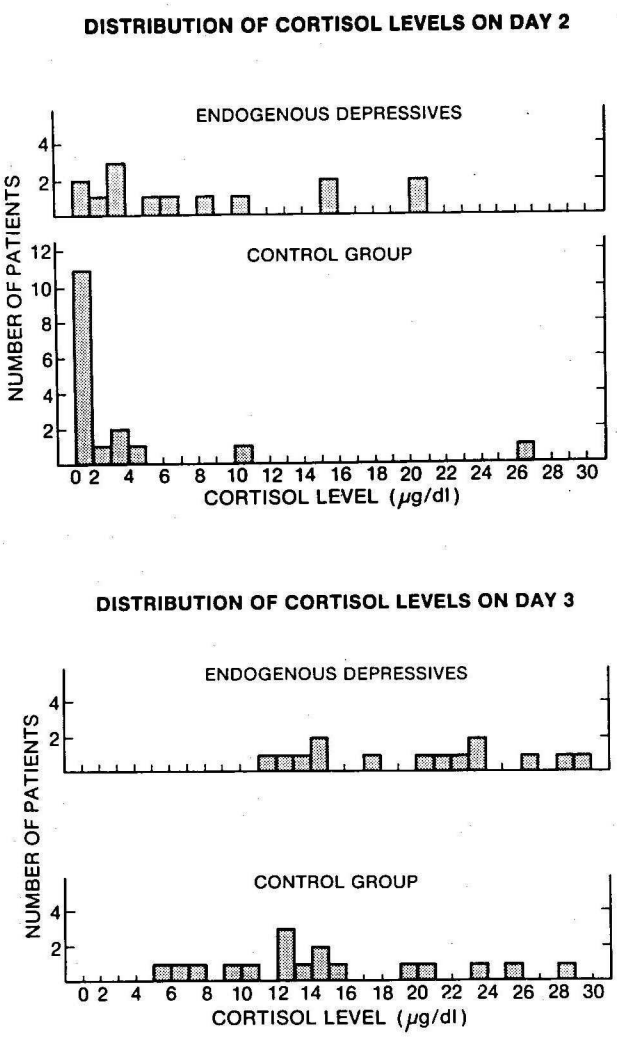

FIG. 1. Distribution of individual cortisol concentrations at 1600 hr on day 2 (top) and at 0800 hr on day 3 (bottom) after dexamethasone administration (1.0 mg at 2300 hr on day 1) in endogenous depressives and controls (other psychiatric inpatients).

sampling (Krieger *et al.*, 1971; McHardy-Young *et al.*, 1967). However, the inhibition of cortisol secretion does not seem to continue beyond the next day (day 2): thus, only three of 20 normal subjects maintained suppressed levels of plasma cortisol (< 6 μg/dl) in the morning of day 3 (Tourigny-Rivard *et al.*, 1981).

Theoretically, a prolongation of the time between dexamethasone intake and blood sampling from day 2 to the morning of day 3 could improve the sensitivity of the test. Indeed, a delay of the blood collection on day 2 from 0800 hr (the usual time of sampling

for the screening of Cushing's disease) to 1600 hr and 2300 hr has already been shown to increase the sensitivity for the diagnosis of endogenous depression (Carroll *et al.*, 1976). Moreover, a morning blood sample is easier to collect (especially in comparison to the 2300 hr sample), particularly in outpatients.

Goldberg (1980a,b) reported the use of a modified DST with blood collection on day 3 as an indicator of safe withdrawal of antidepressants. Dexamethasone (1 mg) was administered orally at 2300 hr on day 1, and cortisol was measured at 0900 hr on day 3. For unclear reasons, non-suppression was defined by a cortisol level higher than 7.0 μg/dl. However, even though this modified procedure was claimed to be 'more sensitive', with the detection of 83% of patients suffering from major depressive disorder, the specificity of the test could not be determined, because no control group was studied. Our results do not support the value of this procedure for the diagnostic confirmation of endogenous depression. Indeed, if the same cut-off limit is used (7.0 μg/dl), the DST became actually more sensitive (to 100%), but with a dramatic loss of specificity (to 18%). The best cut-off level in our sample was much higher (20 μg/dl). Nevertheless, despite a similar sensitivity as with the day 2 sample (57%), both the specificity and diagnostic confidence were substantially lower than on day 2 (76% vs 88% and 67% vs 80%). These results are in agreement with the study of Faber (1983), which included nine DST suppressor and nine DST non-suppressor major depressive patients (non-suppression was defined by cortisol levels higher than 5 μg/dl at 0800 hr, 1500 hr, or 2200 hr on day 2); all subjects had 34 hour cortisol values above 7 μg/dl, and the best cut-off value was 17 μg/dl.

The mean cortisol levels in our subjects were much higher at 0800 hr on day 3 than at 1600 hr on day 2, not only in the endogenous depressive subgroup (where it might be associated with an increase of sensitivity), but also in the control group. The best cut-off level at 0800 hr on day 3 (20 μg/dl) is also the upper limit for normal values in our laboratory. In fact, it is questionable if the cortisol levels at 0800 hr on day 3 differ from basal values. Although our study does not permit an answer to this possibility because no basal cortisol levels before the DST were measured, basal cortisol levels collected in two other studies in comparable samples (Legros *et al.*, 1983; Ansseau *et al.*, 1984) were in the same range as those of the control group (16.72 ± 8.71 μg/dl and 15.37 ± 7.72 μg/dl vs 15.28 ± 7.09 μg/dl; p = NS). Moreover, in two studies wherein baseline 0800 hr samples were collected, mean 34 hour cortisol levels did not differ significantly from basal values (Tourigny-Rivard *et al.*, 1981; Faber, 1983). In the latter study however, DST suppressor depressives were still exhibiting lower cortisol levels on day 3 compared to baseline. Taken together, these findings suggest that the inhibitory activity of dexamethasone is very weak on day 3.

Thus, a morning day 3 cortisol sample after DST appears to be less useful in the diagnostic confirmation of endogenous depression than a late afternoon sample on day 2.

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