The Dexamethasone Suppression Test in Adolescent Outpatients With Major Depressive Disorder

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Objective: The purpose of the study was to determine whether the dexamethasone suppression test (DST) would discriminate between outpatient adolescents with major depressive disorder and normal adolescent comparison subjects. Method: Depressed patients were accepted into the study only if they fulfilled the Research Diagnostic Criteria for major depressive disorder. The depressed subjects (N=44) and the normal subjects (N=38) were studied in the same environment and under the same conditions. The subjects received 1 mg of dexamethasone at 11:00 p.m. The next day, blood for determining plasma cortisol concentrations was drawn through an indwelling catheter every 60 minutes from 8:00 a.m. until 11 p.m. Results: After dexamethasone, the cortisol levels of the adolescents with major depressive disorder and the normal subjects were not significantly different. Only six (14%) of the depressed subjects and one (3%) of the normal subjects showed evidence of nonsuppression (cortisol value greater than 5 μg/dl). Analyses of subgroups of the depressed patients based on suicidal tendencies and endogenous subtype also failed to reveal significant differences in cortisol values. Estimates of the severity of depression showed significant negative correlations with cortisol values among the depressed patients. Conclusions: In contrast with previous studies of adolescent inpatients, the DST did not discriminate between the adolescent outpatients with major depressive disorder and the normal comparison subjects in this study. Possible reasons for the discrepancies, such as severity of the depression and inpatient status, are discussed.

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There has been controversy concerning the role of the dexamethasone suppression test (DST) as a tool for the diagnosis of major depressive disorder in adults, children, and adolescents. Casat et al. (1) reviewed the available studies on the use of the DST in children and adolescents. There were eight studies on adolescents (2–9), with a total of 475 inpatients, of whom 157 (33%) had major depressive disorder. These studies used a prospective design, the Research Diagnostic Criteria, or DSM-III criteria for diagnosis and included one or more control groups. In all of them, 1 mg of dexamethasone was administered at 11:00 p.m. In most of the studies, blood samples for determination of cortisol levels were drawn at 4:00 p.m. and 11:00 p.m. on the day after dexamethasone administration. Casat et al. showed that 74 (47%) of the adolescent inpatient subjects with major depressive disorder and 63 (20%) of the subjects with other psychiatric disorders were nonsuppressors of cortisol ($\chi^2=3.84$, df=1, p<0.0001). When a serum cortisol level of 138 nmol/liter (5 μg/dl) was used as the threshold for nonsuppression, the pooled DST sensitivity and specificity were 47% and 80%, respectively.

Our study adds uniquely to the existing literature on the DST in adolescent major depressive disorder by virtue of the following four main features. 1) It used a large outpatient group of depressed adolescents. 2) Both depressed and normal subjects were studied in the same environment and under the same conditions. 3) After administration of dexamethasone, cortisol levels were determined each hour from 8:00 a.m. to 11:00 p.m. (i.e., 16 times) from blood drawn through an indwelling venous catheter. 4) The majority of these adolescent subjects had also participated in another study of 24-hour baseline cortisol measures, permitting within-subject comparisons of 24-hour baseline cortisol levels with DST cortisol levels.

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METHOD

Patients were accepted for screening at a child and adolescent depression clinic if they were reported to appear sad, said they felt sad, had suicidal ideation or behavior, were nervous or afraid, or displayed ritualistic behavior. After informed consent was obtained, each patient was screened for appropriateness for the study in a 10- to 14-day diagnostic evaluation that included, in the following order, the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode (KIDDIE-SADS-P) (10), the Psychosocial Schedule (11), a pediatric history and examination including Tanner staging (12, 13), and, 10–14 days later, another KIDDIE-SADS-P covering the past week. The second KIDDIE-SADS-P assessment was done without knowledge of the findings of the first. The diagnosis of major depressive disorder was made with the unmodified adult Research Diagnostic Criteria (RDC) (14). The diagnoses of nonaffective emotional disorders conformed to DSM-III criteria.

All subjects were between the ages of 11 and 18 years and had reached at least Tanner stage III of sexual development, as determined by a pediatrician. Depressed subjects were accepted into the study only if they fulfilled the RDC for major depressive disorder (at least probable) in both KIDDIE-SADS-P evaluations. Major depressive disorder was considered to be endogenous only if it fulfilled the RDC for definite endogenous subtype in both evaluations. If not, subjects were classified as having the nonendogenous subtype.

Potential subjects were excluded if they met any of the following criteria: 1) use of psychoactive medication that could affect hypothalamic-pituitary function, 2) significant physical illness, especially endocrinopathies or heart disease, 3) obesity (weight-for-height greater than 95% on the National Center for Health Statistics curve) or growth failure (height or weight lower than the third percentile), 4) clinically diagnosed seizures or other major neurological illness, 5) IQ less than 70, 6) fulfillment of the DSM-III criteria for anorexia nervosa, autism, or schizophrenia, and 8) inordinate fear of needles (needle phobia).

Normal comparison subjects were recruited through personal contacts and informal networking. The exclusion criteria enumerated above were also used for this group. The criterion for inclusion was no current or past history of child psychiatric disorder, as determined by a single KIDDIE-SADS-E assessment (mother and child interviewed independently).

Eighty-two subjects were accepted for the study: 44 patients with major depressive disorder (24 had the endogenous subtype, 19 were suicidal, and four were psychotic) and 38 normal comparison subjects. Two of the subjects had more than two missing data points at the end of the testing and were dropped from the study. There were no significant group differences in age (patients with major depressive disorder: mean=14.9 years, SD=1.9; normal subjects: mean=15.3 years, SD=1.5), sex (patients: 22 female and 22 male; normal subjects: 13 female and 25 male), or race (patients: 28 white, six black, and 10 other; normal subjects: 21 white, eight black, and nine other).

Severity of depression was assessed by examining scores on the KIDDIE-SADS-P and by extracting scores on the 21-item Hamilton Rating Scale for Depression from the KIDDIE-SADS-P scores with an adaptation of the method of Endicott et al. (15). The mean Hamilton depression score for the patients with major depressive disorder was 24.7 (SD=4.3). There was no statistically significant difference in Hamilton depression scores between patients with endogenous major depression (mean=25.2, SD=5.0) and those with nonendogenous depression (mean=24.1, SD=3.1) (t=0.87, df=39, n.s.). The patients with suicidal ideation (score of 4 or more on the KIDDIE-SADS-P item for suicide, indicating a definite plan or attempt) tended to have higher Hamilton depression scores (suicidal, mean=26.1, SD=3.0; not suicidal, mean=23.7, SD=3.4) (t=1.86, df=41, p=0.07). There were significant differences in Hamilton depression scores between the male and female depressed patients (male, mean=23.3, SD=4.3; female, mean=26.2, SD=3.7) (t=2.35, df=41, p=0.02).

After the 2-week diagnostic protocol and acceptance into the study, subjects came to a sleep/neuroendocrine unit to be tested. An indwelling catheter was placed in an antecubital vein, and the vein was kept open by a slow drip of heparinized saline. Blood samples were immediately centrifuged, and the plasma was separated and then frozen.

Plasma cortisol was analyzed by competitive protein-binding radioassay with intra-assay coefficients of variation of 9.1%, 3.7%, and 2.4% at 68.9, 342.1, and 557.3 nmol/liter, respectively, and interassay coefficients of variation of 9.6%, 3.9%, and 4.8% at the same levels.

This study was part of a psychobiological study of children with major depressive disorder that included the following general neuroendocrine and sleep measures: night 1: sleep EEG; day 1: thyrotropin-releasing hormone (TRH) challenge tests; night 2: sleep EEG; day 2: 24-hour test of blood cortisol levels; night 3: sleep EEG; day 3: morning, insulin tolerance test; 3:00 p.m., amphetamine challenge test; 11:00 p.m., administration of 1 mg p.o. of dexamethasone; day 4: testing of blood cortisol levels hourly from 8:00 a.m. until 11:00 p.m. Approximately 90% of the subjects participated in the full protocol. The other 10% participated only in the amphetamine challenge test and the DST. There was no difference in DST results between the latter subjects and those who participated in the full protocol.

A subgroup of 14 subjects (eight patients with major depressive disorder and six normal subjects) participated in an earlier version of the DST protocol with the indwelling catheter, but plasma sampling was done only at 8:00 a.m., 4:00 p.m., and 11:00 p.m. The data of these subjects were included only in the analyses of those time points. Thus, for the 16-hour analysis we included data on only 66 subjects: 35 patients with major depressive disorder (19 endogenous, 16 suicidal, and 10 nonendogenous), 21 normal subjects (17 female and 4 male), and 10 suicidal normal subjects (9 female and 1 male).
three psychotic) and 31 normal comparison subjects. This subgroup of subjects (hereafter referred to as the “reduced group”) participated in all of the studies we have described, and the protocol was in all other ways identical to that for the rest of the group. As in the full group of subjects, there were no significant differences in age, sex, or race between the depressed patients and the normal subjects in the reduced group.

In the statistical analysis, cortisol levels were examined for normality with the W statistic of Shapiro and Wilk (16) and transformed as necessary before testing with parametric techniques. If, after transformation, the measures were still significantly abnormal, nonparametric techniques (e.g., the Mann-Whitney test) were used for between-group comparisons. Spearman correlation coefficients were used to examine the associations between cortisol levels and severity of depression. The problem of missing data was minimal. The two subjects who had more than two consecutive missing samples were excluded from all examinations of the mean 16-hour cortisol levels. One or two missing samples from a single subject were linearly interpolated.

RESULTS

After the administration of dexamethasone, there were no significant differences between the depressed group and the normal group on the following summary variables: mean 16-hour cortisol level, peak cortisol level, and mean cortisol level measured at each of the 16 testing times, including cortisol levels for “standard” testing times (8:00 a.m., 4:00 p.m., and 11:00 p.m.) (table 1, figure 1). Repeated measures analysis of variance with the Greenhouse-Geisser adjustment (17) showed a significant effect of time (F=4.4, df=4.4, 284.4, p=0.002) but not a significant Time by Diagnosis interaction (F=1.05, df=4.4, 284.4, p=0.40). There was no significant difference between the depressed patients and the normal subjects in the percentage of samples with cortisol values of 138 nmol/liter (5 μg/dl) or more. These summary cortisol variables and the percentage of samples with cortisol values of 138 nmol/liter or more also failed to discriminate among the subgroups of patients with major depressive disorder (suicidal, endogenous, and psychotic). Contrary to our expectation that patients with more severe depression would show higher postdexamethasone plasma levels of cortisol, we found a negative correlation between severity of depression and mean 16-hour cortisol level (r=-0.46, N=34, p=0.006), peak cortisol level (r=-0.50, N=34, p=0.003), 4:00 p.m. cortisol level (r=-0.43, N=43, p=0.004), 11:00 p.m. cortisol level (r=-0.30, N=43, p=0.06), and mean cortisol level for blood samples taken at 8:00 a.m., 4:00 p.m., and 11:00 p.m. (r=-0.40, N=43, p=0.02).

Exploratory analyses of covariance revealed no significant effects of age, sex, or the Age by Sex and Age by Diagnosis interactions on any of the summary cortisol variables for the full study group. Within the reduced group, the female subjects had significantly higher hourly and mean 16-hour postdexamethasone cortisol levels than the male subjects (female: mean=28.1 nmol/liter, SD=19.3; male: mean=23.9 nmol/liter, SD=33.5) (U=705, p<0.02).

In addition to the continuous variable analyses, we explored categorical comparisons of our data with data from clinically based studies that used the concept of a cutoff value to indicate nonsuppression of cortisol. We chose a standard cutoff of 138 nmol/liter (5 μg/dl) at any of the three usual time points (8:00 a.m., 4:00 p.m., and 11:00 p.m.) to define nonsuppression. This revealed that six of the 44 patients with major depressive disorder were nonsuppressors, compared to one of the 38 normal subjects (p<0.20, Fisher’s exact test). Comparison of clinical variables (Hamilton depression scores, endogenous subtype, sex, suicidality, and age) between the nonsuppressors (N=6) and the rest of the group with major depressive disorder (N=38) revealed no significant differences.

Approximately 90% of the subjects in this research
also participated in a study of 24-hour baseline cortisol secretion. In that study, Dahl et al. (18) reported no significant differences in the peak, nadir, or time of the nocturnal rise of plasma cortisol between patients with major depressive disorder and normal subjects. We examined the relation between the mean 24-hour baseline cortisol levels from that study and the postdexamethasone mean 16-hour cortisol levels in this study and found a significant positive correlation ($r_s=0.54, N=64, p<0.0001$).

We used receiver operating characteristic analysis (19) to explore the sensitivity and specificity of the DST. This curve is a standard way of showing the various possible pairs of test sensitivity (rate of true positives) and specificity (1 minus the rate of false positives) at various cutoff scores. We analyzed the mean 16-hour, peak, 8:00 a.m., and 4:00 p.m. cortisol values for 100 cutoff scores (from 0.0 nmol/liter to 220.7 nmol/liter). All of the receiver operating characteristic curves obtained were not significantly different from the expected random receiver operating characteristic curve. (Figure 2 shows the receiver operating characteristic curve for cortisol values at 4:00 p.m.) For comparison with other studies, we also used 138 nmol/liter (5 μg/dl) as the cutoff cortisol value to define nonsuppression.

With this cutoff level, the sensitivity and specificity for 8:00 a.m. and 4:00 p.m. were 9.0% and 100%, respectively. Sensitivity and specificity were identical when 4:00 p.m. values were used.

DISCUSSION

In contrast with previous inpatient adolescent studies, the DST in our sample of outpatients did not discriminate between patients with major depressive disorder and normal comparison subjects. Similarly, our group has also reported (20) that in a large group of prepubertal subjects with major depressive disorder (predominantly outpatients), the DST did not discriminate among subjects with major depressive disorder, those with nonaffective psychiatric disorders, and normal subjects.

The reason for these discrepancies with previous reports on inpatients is not clear. Possible factors contributing to positive findings with inpatient subjects include 1) severity of depression in the subjects being studied and 2) stress induced by the hospitalization.

In adults, high rates of DST nonsuppression are associated with greater scores on severity of depression (21). Because of this association, one must consider possible differences in severity as contributing to the negative results in this study. Our results in adolescents do not support this explanation. Our overall study group had Hamilton depression scale scores indicating moderate to high severity. Further, in contrast with the reports on the DST with adults, the correlation between severity scores and post-DST cortisol levels was negative. Thus, it appears unlikely that severity is the sole answer to these discrepancies, at least in the adolescent age group.

We believe that a second important source of variance, potentially contributing to differences between the results of our studies and the existing literature on depressed inpatient adolescents, is the stress of hospitalization. The relatively low-stress environment in our sleep laboratory (to which the adolescents had adapted during the psychobiological protocols) may not have been sufficient to uncover a vulnerability to stress associated with depression. In previous studies, the stress of being on an inpatient unit may have contributed to the positive DST findings.

Stress such as surgery, preoperative surgery procedures, examinations, and admission to the hospital may trigger a large transient rise in cortisol production (for reviews of this subject see 22, 23). To our knowledge there are no studies of adolescents that have directly addressed this issue. The few studies of children have shown the same trends. For example, Tennes and Kreye (24) showed that grade-school subjects had significantly higher urinary cortisol levels on mornings when classroom examinations were scheduled than on other days. Knight et al. (25) demonstrated that children, particularly those who denied stress, had significantly increased urinary cortisol secretion after admission to the hospital for elective surgery. Barnes et al. (26), studying children undergoing open heart surgery, found that urinary 17-hydroxycorticosteroids were significantly elevated on the day before surgery and on the day of return from intensive care.

It is likely that stress increases the rate of nonsuppression of cortisol after administration of dexamethasone. There are no studies of stress-induced nonsuppression of cortisol on the DST in children or adolescents. In adult psychiatric and medical patients, hospitalization has been found to induce an increase in the rate of nonsuppression on the DST in the first 48 hours after admission (21). Culemans et al. (27) administered the DST to 40 presurgical patients and 20 normal control
subjects. They found that all of the control subjects were suppressors, but 47.5% of the presurgical patients were nonsuppressors. Blumenfield et al. (28) found impaired urinary 17-hydroxycorticosteroid suppression after dexamethasone administration in military trainees under stress. Baumgartner and Kurten (29) showed that depressed patients, schizophrenic patients, and normal volunteers under stress (giving a lecture) had similar rates of cortisol nonsuppression (36.5%, 50.0%, and 43.8%, respectively).

The indwelling catheter itself may also cause stress; however, in this study the blood samples were drawn after subjects had adapted to the laboratory environment and the indwelling catheter. Another group of subjects in the same laboratory, who were following similar protocols, were assessed for stress. They indicated that the degree of subjective stress was quite low and that the indwelling catheter as a rule caused little discomfort (30). In previous studies, subjects experienced the combined stress of repeated venipunctures and the hospitalization process (particularly when the DST was done shortly after admission). In some studies, these combined stresses may have interacted to produce nonsuppression.

In summary, stress increases baseline cortisol levels as well as nonsuppression of cortisol on the DST. It may contribute to the differences in the results of inpatient and outpatient investigations that we have described.

In this study, we found a negative correlation between severity of depression and cortisol level. Thus, patients with high Hamilton depression scores had lower post-DST cortisol levels. This finding is the opposite of what we expected and needs further exploration.

One limitation of this study was that serum dexamethasone levels were not ascertained. Several studies of adults with major depressive disorder have reported a significant negative correlation between cortisol and dexamethasone levels (31–35), suggesting that cortisol nonsuppressors have a lower level of plasma dexamethasone than cortisol suppressors. Naylor et al. (36) studied 73 inpatient children aged 5–14 years and found that overall, DST nonsuppressors had significantly lower plasma dexamethasone levels than suppressors; similar nonsignificant trends were observed in the depressed subjects. In addition, our group (20) studied 24-hour plasma levels of dexamethasone in children with major depressive disorder and found no statistically significant difference in dexamethasone levels between the suppressor and nonsuppressor depressed patients and also no difference between the depressed patients, the patients with nonaffective psychiatric disorders, and the normal subjects.

A second potential limitation of this study was the dose of dexamethasone administered. It is possible that a lower dose might have improved the sensitivity of the DST in this group of patients. However, to our knowledge there have been no studies comparing dexamethasone dosages in adolescents. Only two studies of children have addressed this issue. Doherty et al. (37) investigated dose response and reported that there were no significant differences in the percentages of children who were nonsuppressors in response to low, medium, and high doses of dexamethasone based on body weight. On the other hand, Naylor et al. (36) did not find a correlation between milligram-per-kilogram dexamethasone dose and plasma dexamethasone concentration, but they did find a significant correlation with body surface area.

Although our data suggest that the DST may not have clinical utility, there may be research value in delineating a biologically distinct subgroup of depressed subjects who do not suppress cortisol on the DST. Particularly with young subjects, the long-term follow-up of this biologically distinct subgroup may provide essential information. Along these lines, we have some follow-up data that concern our subjects, although they did not have systematic clinical follow-up. Rao et al. (38) recently began the process of identifying and following up a wide range of children and adolescents initially studied by the Puig-Antich et al. group, including adolescents from the present study. Rao et al. have located approximately 78% of the subjects with major depressive disorder across studies and have found that eight committed suicide. Three of those eight were subjects in this study, two of whom had shown nonsuppression of cortisol on the DST. Although this is primarily an anecdotal observation (not a statistically significant finding), it is provocative that at least two of the six nonsuppressors committed suicide. This finding is also interesting because of previous reports that suicidal ideation was correlated with high basal cortisol secretion near sleep onset in adolescents with major depressive disorder (39), high urinary free cortisol (40), and nonsuppression of cortisol on the DST (41–45). Controlled longitudinal follow-up studies in combination with the DST and other biological measures will be needed to address this relationship.

In conclusion, both baseline cortisol levels (18) and cortisol levels after dexamethasone in the adolescents we studied failed to show significant group differences, suggesting that the hypothalamic-pituitary-adrenal axis was functionally normal in the overall sample of depressed adolescents. There was a small subgroup of nonsuppressors who did not appear to be clinically distinct from the rest of the group with major depressive disorder. Clinical follow-up of this group may help to delineate the possible role of the DST as a research tool.

REFERENCES


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