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The Dexamethasone Suppression Test in Children: Lack of an Association with Diagnosis

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The dexamethasone suppression test was carried out on 44 children to assess agreement with diagnosis of depression. No significant association was found between suppression of plasma cortisol and depression diagnosed clinically or by cluster analysis.

Over the last decade, the Dexamethasone Suppression Test (DST) has been used to distinguish adult patients with endogenous depession from those with neurotic depressive conditions (Carroll *et al*, 1981; Dam *et al*, 1985). Dexamethasone is a synthetic corticosteroid which suppresses adrenocorticotropic hormone (ACTH) and cortisol secretion in normal subjects. Within a sample of depressed patients, those with endogenous depression, particularly if accompanied by melancholia, have been shown to have raised values of plasma cortisol following administration of dexamethasone 17–24 hours earlier (Arana *et al*, 1985). This is not an all-or-nothing phenomenon; there is a relative resistance to the effects of dexamethasone in depression. Patients who exhibit escape of plasma cortisol following dexamethasone (positive DST) are less likely to respond to cognitive and other non-pharmacological treatments for depression although this is a controversial area (Rush, 1984; Brown *et al*, 1987). The potential value of the DST in child psychiatry is apparent, particularly in prepubertal children.

A few studies of relatively small samples of patients have shown that a clinical diagnosis of endogenous depression in prepubertal children is associated with a positive DST (Puig-Antich, 1980; Poznanski *et al*, 1982; Weller *et al*, 1985; Petty *et al*, 1985; Woodside *et al*, 1987). Others have not found a clear relationship between the diagnosis of depression and a positive DST and are doubtful about the specificity of the test in children (Livingstone *et al*, 1987; Ha *et al*, 1984). As the diagnosis of depression in prepubertal children is difficult to establish, this controversy is not surprising.

The purpose of this study was to examine the relationship between the diagnosis of depression in children and plasma cortisol values following dexamethasone administration, and to compare these with results in non-depressed children.

Method

The design and rating instruments used are described in an accompanying paper (Kolvin *et al*, 1991). This paper is concerned with the first 50 patients that were assessed as part of this investigation. None of these patients were receiving anti-convulsants, hypnotics, antidepressant drugs or any other medication. No patient had any major medical condition or endocrine abnormalities and no child was suffering from anorexia nervosa.

After the initial interview with the child by the psychiatrist, but before administration of the schedules and scales, the parent and the child were invited to participate in the research and asked if a blood sample could be taken in order to provide more information about the diagnosis. It was emphasised that this was a research procedure. If consent was obtained from the child and parent, the parent was asked to give 0.5 mg or 1 mg of dexamethasone to the child according to weight: children weighing 49 kg or more received 1 mg of dexamethasone; those with a weight below this figure received the lower dose. This was to ensure as far as possible that the dosage of dexamethasone given was of the order of 15 μg/kg per patient as used in previous studies with children (Poznanski *et al*, 1982; Robins *et al*, 1983; Petty *et al*, 1985). It would have been ideal if exactly the same dose/kg of dexamethasone was given to all subjects. However, as dexamethasone tablets are only available in 0.5 mg and 1 mg strengths this was not possible.

The child (and parents) were instructed to take the tablet(s) of dexamethasone as near as possible to 10.00 p.m. that evening. The next afternoon at 3.00 p.m. the patient returned to the hospital to have blood taken for plasma cortisol. The reason for choosing 10.00 p.m. was to avoid the interruption in sleep that the 11.00 p.m. administration would have necessitated – stress has been shown to cause increased escape of cortisol following dexamethasone administration (Baumgartner *et al*, 1985; Ceulemans *et al*, 1985). For the same reason, blood tests were taken within one week of the interview with child and parent so as to avoid the stress of first out-patient attendance. Samples were collected in lithium heparin tubes and spun down within two hours of collection.

Analysis was by means of radioimmunoassay (Amerlex Cortisol RIA kit, Amersham International PLC, Bucks,

Table 1
DST status and diagnosis of depression on the rating scales and schedules

Observer scales	% of patients exhibiting cortisol non-suppression (plasma cortisol > 108 nmol/l)	
	Positive score on Rating Instrument	Negative score
Standardised psychiatric interview (Depression)	46	56
Standardised psychiatric interview (Anxiety)	48	53
Joint clinical rating	46	56
Kiddie-SADS (Endogenous subtype)	57	43
Weinberg	48	52
Newcastle diagnostic criteria	48	54

Table 2
Relationship between DST results and diagnosis by cluster analysis

Clusters	Cortisol suppression (< 108 nmol/l)	Cortisol non-suppression (> 108 nmol/l)
Endogenous	8	7
Depressive cognitions	7	7
Mixed maladjusted	7	8

Table 3
Relationship between DST results, diagnosis of depression on Kiddie-SADS and patient status

	Cortisol suppression (< 94 nmol/l)	Equivocal cortisol suppression (94-122 nmol/l	Cortisol non-suppression (> 122 nmol/l)	Total
	17 hours after dexamethasone (% of cases showing non-suppression)			
Not depressed	6	1	5 (42)	12
Depressed but not endogenous	6	2	3 (27)	11
Endogenous depression	8	3	10 (48)	21
Total	20	6	18	44

Table 4
Relationship between demographic features and DST results

	Cortisol suppression (< 108 nmol/l)	Cortisol non-suppression (> 108 nmol/l)
Mean age: years (s.d.)	12.7 : (2.0)	12.9 : (1.8)
Sex (male:female)	10 : 12	10 : 12
Pre-pubertal: post-pubertal	11 : 11	12 : 10

UK). The intra-assay coefficient of variation for serum cortisol between 70 and 200 nmol/l was 3% and the inter-assay variation 7%. The child and parent were both asked at the time of the blood sample whether the child had taken the dexamethasone tablet(s) the previous night. If there was doubt whether the tablets had been taken at the recommended time and in the correct dosage the test was repeated and the second result taken as the correct one. This only occurred on one occasion.

Of the first 50 patients entering the study, 44 completed the test satisfactorily. With the remaining six, two children refused venepuncture, in three the blood specimen was broken in transit or in the laboratory, and in one subject blood samples were not taken because the correct procedures for the test were not carried out and it was not possible to repeat these.

The original intention in the study was for 100 subjects to be examined by the DST. To determine the usefulness of this test the results were analysed after half of the intended sample had been seen. The results presented below persuaded us that further testing was unlikely to be fruitful.

Results

Of the 44 patients, 22 did not suppress plasma cortisol after dexamethasone (cortisol > 108 nmol/l) 17 hours after administration of dexamethasone. The relationship between the diagnosis of depression on the various instruments and the DST results is indicated in Table 1. The criteria for a positive score on the rating instrument are those of the designers of the scale concerned. Table 2 shows the results of the DST in children diagnosed according to the cluster analysis described in an accompanying paper (Kolvin *et al*, 1991).

Although there is a hint of patients with endogenous features to display non-depression of plasma cortisol, there is no significant difference between DST status and diagnosis of depression whichever set of diagnostic criteria is used to establish this.

As the appropriate 'cut-off' level for determining suppression of serum cortisol following dexamethasone administration in children is not known for certain, the post-dexamethasone cortisol levels were correlated with the diagnosis of depression on all the instruments used. The correlations varied from $r = -0.19$ on the SPI (Anxiety) to $r = +0.23$ on the Kiddie-SADS (Pearson correlation). None of the correlations were significant.

We used the criterion value of 108 nmol/l for plasma cortisol because previous work has shown that best discrimination between endogenous and non-endogenous adult depressive patients was achieved at this level (Holden, 1983). As the interassay variation for measurement of plasma cortisol in this laboratory was 7% it can be argued that children with cortisol levels between 94 and 122 nmol/l have equivocal suppression of cortisol. The relationship

between diagnosis of depression and cortisol suppression according to this stratification is illustrated in Table 3. The demographic details of the children involved according to the cortisol suppression status are listed in Table 4.

In addition, the relationship between DST status and symptoms was examined by comparing the DST results with the presence or absence of the 23 major symptoms identified during the interviews with child and parents, as well as with age, sex and presence or absence of pubertal changes according to Tanner's criteria (Tanner *et al*, 1965). The only symptom that significantly separated dexamethasone suppressors and non-suppressors was the summated obsessive-compulsive score (higher in the non-suppressors). This could very well be a chance finding in view of the number of factors examined.

Discussion

The results show that there is little relationship between the effects of dexamethasone on plasma cortisol levels and the diagnosis of depression, however this is established. There is a trend for cortisol non-suppressors to be endogenously depressed but this is barely shown by the existing schedules for measuring depression in children nor by the classification according to cluster analysis.

What other factors could explain these results? It is theoretically possible that some of the patients with high cortisol levels did not actually take their dexamethasone tablets on the evening of the test and therefore the results were artificially high. We do not believe that this is likely. Each patient was asked whether he had taken his dexamethasone tablet(s) the night before and at what time, and this information was confirmed with the parent. The child was aware that the blood test would not be taken unless the tablet(s) had been swallowed so there was little incentive to mislead the doctor. After extensive interviews with both the parent and child, a good alliance had been established between the doctor and patient and the importance of taking the tablet was emphasised.

Measurement of dexamethasone concentration in the blood sample was considered but was not performed. At the time the survey was carried out, assay methods to detect dexamethasone at low concentrations were complex and had limited sensitivity (Chan *et al*, 1980). Since then, reliable assays have become available and both false positive and false negative results may result because of the varying bioavailability of dexamethasone (Meikle *et al*, 1975; O'Sullivan *et al*, 1989). This being said, Hindmarsh & Brook (1985) have shown that a dose of dexamethasone lower than used in this study (0.3 mg/m^2) was effective in suppressing serum cortisol in all six children given this dose. The lowest dose received in our study was 0.34 mg/m^2.

We used a modification of the recommended procedure for carrying out the DST in out-patients. In adults, the dexamethasone tablets are normally administered at 11.00 p.m. on the night before the test is carried out and blood is taken at 4.00 p.m. the next day. The sleep-wake cycle of children and adolescents is substantially different from adults and it is known that the diurnal variation of cortisol secretion is closely related to this cycle (Sherman *et al*, 1984). We therefore asked the parent to administer the tablet at 10.00 p.m. and blood was taken at 3.00 p.m. the next day. Hindmarsh & Brook (1985) have shown that suppression of serum cortisol is achieved in prepubertal children when dexamethasone is administered at 10.00 p.m. Because the circadian rhythms of children vary from adults, we selected 3.00 p.m. for measurement of plasma cortisol. It has been shown that an interval of 17 hours between administration of dexamethasone and estimation of plasma cortisol provides most satisfactory discrimination between suppressors and non-suppressors (Carroll *et al*, 1981; Weller *et al*, 1985).

Non-suppression of cortisol secretion following dexamethasone has been shown to correlate directly with age in adult subjects (Feinberg & Carroll, 1984; Rosenbaum *et al*, 1984). In virtually all the prepubertal children we used a dexamethasone dose of 0.5 mg. This dose was found to provide best discrimination between depressed and non-depressed prepubertal children in a recent study (Pfeffer *et al*, 1989). Older patients with a weight of more than 49 kg were given two tablets of dexamethasone (1 mg) in order to achieve a similar dose/kg to the younger children. Because most of the children were only a little over 50 kg, the mean dose (s.d.) of dexamethasone received by the children who took 1 mg of dexamethasone was 17.8 (2.4) μg/kg, whereas those who had the 0.5 mg tablet received 14.2 (2.2) μg/kg, a significant difference (F-ratio 13.6; $P = (0.001 - \text{analysis of variance})$). The mean 17-hour cortisol value (s.d.) was 164 (179) for the 33 children who received 0.5 mg of dexamethasone and 107 (79) for the 11 who received 1 mg. This difference is not significant (F-ratio 1.02; $P > (0.1 - \text{analysis of variance})$), and is partly accounted for by an extreme outlier in the lower dosage group (860 nmol/l). Indeed, the mean dose of dexamethasone (s.d.) received by those who had cortisol values above 108 nmol/l of serum cortisol was virtually identical to the suppressors (15.6 (2.9) μg/kg c.f. 15.1 (2.9) μg/kg).

The criterion level for determining an abnormal dexamethasone suppression test remains a subject for controversy. In theory, radio-immunoassay methods

should be more sensitive at detecting plasma cortisol than competitive protein-binding methods with consequent reduction of the cut-off level for determining an abnormal result. In practice this is not the case (Ritchie *et al*, 1985). Many laboratories accept the criterion value of 138 nmol/l (5 g/dl) as the limit for non-suppression of plasma cortisol. Recent work from the same laboratory where our test was carried out showed that the diagnostic confidence of the test was optimal when a criterion value of 108 nmol/l of plasma cortisol was selected in adult patients (Holden, 1983) so we have selected this cut-off value.

Although the numbers are not great, our study does not indicate that the DST is more accurate in distinguishing depression in adolescents than in prepubertal children. There is the merest suggestion that endogenous depression, defined according to Kiddie-SADS, is associated with cortisol non-suppression in the pubertal children. Seven of the 10 children rated as endogenous were DST positive, whereas 4 of the 11 children with insufficient symptoms of endogenicity also showed failure to suppress plasma cortisol. With the prepubertal children there was no relationship at all between the diagnosis of endogenous depression and DST status with equal number of children occurring in all four groups in the $2 \times 2 \chi^2$ table.

Although some studies of the DST in prepubertal children have shown the test to be of value in identifying patients with depression (Puig-Antich, 1980; Poznanski *et al*, 1982; Weller *et al*, 1985) some recent investigations have shown the test to have much lower specificity. Petty *et al* (1985) found in a study of 30 pre-pubertal children admitted to a psychiatric hospital that five out of six patients who had no evidence of depression were DST positive. Livingstone & Martin-Canicci (1987) also raised doubts about the specificity of the test, finding that patients with separation anxiety also had a high incidence of cortisol non-suppression.

Our results indicate that the DST is not of great value in identifying depression in children attending an out-patient clinic. They show a high rate of non-suppression of plasma cortisol irrespective of the diagnosis of depression however this is classified. This study supports the conclusions of a review of the status of the DST in children that its validity as a diagnostic test remains in doubt (Leckman, 1983).

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