Indian Journal of Psychiatry, April 1988, **30**(2), pp. 153-159

ADRENOCORTICAL DYSFUNCTION IN DEPRESSION: RESPONSE TO DEXAMETHASONE SUPPRESSION TEST - A COMPARATIVE STUDY[1]

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SUMMARY

Thirty patients of Major Depressive Disorder, Schizophrenia and normal healthy controls each, received an overnight dexamethasone suppression test. Plasma and urinary cortisol measurements showed that depressed patients had increased adrenocortical activity before dexamethasone and they showed an abnormal early escape from suppression which had a relationship with severity of depression. An attempt has been made to differentiate depressives from schizophrenics by abnormally high cortisol values. Post-dexamethasone urinary cortisol as well as combined urinary cortisol and plasma cortisol abnormal values gave the best pointers of differentiation. A non-significant trend of higher values was observed in bipolar and retarded depressives. Schizophrenics did not differ from normals at any stage.

Introduction

Considerable research findings have accumulated over the last two decades regarding the role of the dexamethasone suppression test (DST) as a specific diagnostic test in endogenous depression. Carroll (1982) has summarized research in this area and has shown that about 40 - 50 per cent of patients suffering from primary depression have an abnormal DST. An attempt is going on all over the world to find clinical differences between suppressors and non-suppressors. Carroll and Davies (1970), Brown et al. (1979), Saleem (1984), Ames et al. (1984) have not found any symptomatic difference between suppressors and non-suppressors. Some studies have shown a relationship between non-suppression and poor response to anti-depressant medication (McLeod et al. 1972; McIntyre et al. 1981).

In the present study an attempt has been made to examine the basic adrenal activity, diurnal rhythm of cortisol secretion and response of DST in depressed patients. Clinical differentiation has been made by looking at the severity of depression and comparing uni-polar versus bi-polar depressives and agitated versus retarded depressives. Schizophrenics and normal healthy persons have been taken as two control groups.

Material and Methods

The study was conducted on 30 definite cases of 'Primary Major Depressive Disorder' diagnosed according to research

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1. Paper presented at the 33rd Annual Conference of Indian Psychiatric Society, held at Ahmedabad in Dec., 1980.

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diagnostic criteria (RDC) (Spitzer et al. 1978) at the Department of Psychiatry, Institute of Medical Sciences, Banaras Hindu University. Thirty Schizophrenics having either acute or subacute onset also diagnosed according to RDC and 30 normal healthy subjects comparable with the depressives comprised the control groups. All the depressive patients were assessed on Hamilton Rating Scale (HRS) for severity of depression (Hamilton 1967).

There were 24 males and 6 females with the mean age of 32.2 years in depressive group. In schizophrenics and normals there were 26 males and 4 females in each with the mean age of 34.3 years and 32.9 years respectively. Maximum number of cases were in the age group of 20 - 44 years. Patients suffering from any physical disorder, having received ECT within the past 6 months, those who could not be kept drug free for seven days and those whose consent could not be obtained either from them or their relatives were excluded from the study.

After 7 days of drug free stay in the hospital, during which time only Nitrazepam tablet 10 mg as hypnotic and some laxative to those who required it as well as placebo tablets to all the patients were given, collection of blood and urine samples were carried out starting from 2330 hours consecutively for 2 days. At the end of day one at 2330 hours 2 mg of oral dexamethasone was given to each patient after the collection of samples. Three 5 ml blood samples in heparinised syringes were collected at 0800 hours, 1600 hours and 2330 hours on each day, which were immediately centrifuged and plasma kept under refrigeration. Twenty four hours urine collection started at 2330 hours on day one and day two each separately which was measured and 20 ml sample kept under refrigeration. Plasma was analysed for plasma cortisol (11 OHCS) by the fluorimetric method of Mattingly (1962) and urinary free cortisol (11 OHCS) by the technique of Mattingly et al. (1964), at Surgical Research Laboratory, Banaras Hindu University. Analysis was done usually within two weeks of sample collection.

Statistical Analysis

The following measured values were log transformed before means and group differences were calculated: Urinary free cortisol (UFC) before and after dexamethasone, each plasma cortisol level after dexamethasone and the midnight plasma cortisol level before dexamethasone. With log transformed values a geometric mean and geometric standard deviation range were obtained. For plasma cortisol values at 0800 hrs. and 1600 hrs. on day one arithmatic mean was calculated. Student's two tailed 't' test was applied either to the log mean or the arithmatic mean.

Highest values of plasma cortisol and UFC at different time seen in normal controls were taken as the cut off point and values above this were treated as abnormal values in depressives and schizophrenics. Chi-square test was applied to see the significance of the frequencies of occurrence of abnormally high levels. The confidence level at which depression could be diagnosed was calculated by the formula (Carroll et al. 1976):

$$\frac{N \text{ (Depression)}}{N \text{ (Depression)} + N \text{ (Schizophrenics)}} \times 100.$$

Where N = Number of patients having abnormal value.

Results

Plasma Cortisol:– On day one depressives had significantly higher levels as com-

Table 1
Mean Plasma Cortisol levels at 0800 hrs, 1600 hrs and 2330 hrs on day one

Group	At 0800 hrs (μg/100 ml)	At 1600 hrs (μg/100 ml)	At 2330 hrs Log Mean ± S.D. (Geometric Mean (S.D. range)) (μg/100 ml.)
Depression	22.17 ± 6.94	16.94 ± 6.56	1.03 ± 0.25 (10.76 (4.5 – 34.2))
Schizophrenia	20.94 ± 6.04	13.77 ± 4.89	0.82 ± 0.22 (6.588 (3.1 – 28.2))
Normals	20.68 ± 6.32	14.45 ± 3.88	0.77 ± 0.14 (5.912 (3.0 – 10.0))

Statistical Analysis:

	At 0800 hours		At 1600 hours		At 2330 hours	
Groups Compared	't'	P	't'	P	't'	P
Depression v/s normals	0.8558	NS	1.7922	NS	5.0162	<0.001
Depression v/s Schizophrenia	0.7283	NS	2.1220	<0.05	3.5120	<0.001
Schizophrenia v/s normals	0.1628	NS	0.5935	NS	0.9652	NS

Table 2
Mean Plasma Cortisol levels on day two (after dexamethasone administration) Log mean ± S.D. (Geometric mean (S.D. range)) in μg/100 ml.

Group	At 0800 hours	At 1600 hours	At 2330 hours
Depression N = 30	0.82 ± 0.23 (6.62 (4.5–33.0))	0.91 ± 0.27 (8.06 (4.3 – 35.0))	0.95 ± 0.27 (8.99 (4.0 – 34.2))
Schizophrenia N = 30	0.68 ± 0.13 (4.75 (2.0 – 28.1))	0.74 ± 0.21 (5.60 (3.0 – 28.0))	0.75 ± 0.21 (5.68 (3.2 – 28.1))
Normals N = 30	0.65 ± 0.13 (4.47 (1.75 – 6.5))	0.66 ± 0.13 (4.55 (1.9 – 7.1)	0.67 ± 0.12 (4.63 (1.9 – 7.0))

Statistical Analysis:

	At 0800 hours		At 1600 hours		At 2330 hours	
Groups compared	't'	P	't'	P	't'	P
Depression v/s normals	3.5606	<0.001	4.4879	<0.001	5.3103	<0.001
Depression v/s Schizophrenia	3.0152	<0.01	2.6750	<0.01	3.1670	<0.01
Schizophrenia v/s normals	0.7988	NS	1.8562	NS	1.9833	NS

pared to both the controls at 2330 hrs., and to schizophrenics at 1600 hrs. (Table 1). In response to dexamethasone all the three groups showed suppression of plasma cortisol levels on day two, but the normals showed maximum suppression and the suppressive effect was maintained upto 2330 hrs. in normals and schizophrenics. In depressives least suppression and a considerable change in the levels by 2330 hours was noticed. (Table 2).

Urinary Free Cortisol On both day one and day two depressives had significantly higher levels of UFC (Table 3). The difference could not have been due to urinary volume change as no significant difference between the mean 24 hours

Table 3
Mean 24 hours urinary 11–OHCS levels on day one and two (Log mean ± S.D. [Geometric mean (S.D. range)) in μg/24 hrs.

Group	On day one	On day two
Depression N = 30	2.70 ± 0.35 (504.7 (99.4 – 1515.6))	2.18 ± 0.45 (151.8 (20.3 – 1125.1))
Schizophrenia N = 30	2.35 ± 0.23 (222.4 (76.5 – 495.5))	1.79 ± 0.19 (61.35 (20.9 – 105.5))
Normals N = 30	2.25 ± 0.25 (177.3 (75.25 – 399.2))	1.74 ± 0.23 (54.74 (20.0 – 102.0))

Statistical Analysis:

	Day one		Day two	
Groups compared	't'	p	't'	P
Depression v/s normals	5.7917	<0.001	4.7828	<0.001
Depression v/s Schizophrenia	4.6405	<0.001	4.3948	<0.001
Schizophrenia v/s normals	1.5864	NS	0.8994	NS

Table 4
Frequencies of abnormal cortisol values in depression and schizophrenia

Timeand Day	No. (%ge) of patients above criterion		Chi-square	P	Confidence* levels (%)
	Depression N = 30	Schizophrenia % B 30			
Before Dexamethasone					
Plasma cortisol at:					
0800 hrs >38 μg/100 ml	0	0	–	–	–
1600 hrs 25μg 100 ml	3 (10)	2 (6.6)	0.22	NS	60
2330 hrs > 10 μg/100 ml	16 (53.33)	6 (20)	7.18	<0.01	72.72
Urinary 11-OHCS > 400 μg/24 hrs.	15 (50)	3 (10)	11.43	< 0.001	83.33
After Dexamethasone					
Plasma cortisol at:					
0800 hrs > 6.5 μg/100 ml	3 (10)	1 (3.33)	1.07	NS	75
1600 hrs > 7.1 μg/100 ml.	11 (36.66)	3 (10)	5.96	< 0.02	78.57
2330 hrs > 7 μg/100 ml	15 (50)	3 (10)	11.43	< 0.001	83.33
Urinary 11–OHCS > 102 μg/24 hrs.	22 (73.3)	2 (6.66)	27.78	<0.001	91.66
Urinary 11–OHCS + any plasma cortisol value above criteria	14 (46.66)	1 (3.33)	15.02	<0.001	93.33

* Percentage of patients above criterion classified correctly as depressed.

urine output was seen in all the three groups.

Discriminatory Value The confidence level at which a given patient with abnormal plasma cortisol value could be diagnosed as depressive ranged from 60% to 93.3% (Table 4). On day one at 2330 hrs. 53.3% of depressives could be diagnosed at a confidence level of 72.7% but at this time 20% of schizophrenics were also having abnormal values. The cortisol values after dexamethasone were a better criterion for discrimination. It is apparent from the table that as the day passed more and more number of depressives showed abnormal plasma cortisol values and at 2330 hrs. 50 per cent of the depressives could be diagnosed at a confidence level of 83.3%. Urinary 11 OHCS levels gave a further better index of discrimination whereby 73.3 per cent of depressives could be diagnosed at a confidence level of 91.6 percent on day two. When the patients having abnormal plasma cortisol value as well as abnormal urinary 11 OHCS value both on day two were compared 46.6 per cent of the depressives could be diagnosed at a confidence level of 93.3 per cent. One schizophrenic patient was also having combined abnormal values, but it was seen that this patient was having urinary 11 OHCS level of 105.5 μg/24 hours, only slightly higher than the cut off point and for all practical purposes this patient could be thought of as having no abnormal urinary 11 OHCS level, in which case 46.6 per cent of depressives could be diagnosed at a confidence level of 100 per cent.

All the patients who had shown abnormal values after dexamethasone were having plasma cortisol values of more than 10 μg/100 ml at 2330 hrs. on day one.

Unipolar v/s Bipolar and Agitated v/s Retarded Depressives

Higher levels of plasma cortisol and UFC were seen at all the times in bipolar and retarded depressives as compared to unipolar and agitated depressives, though the differences did not reach any statistically significant level at any time.

Relationship with severity of depression

Patients having higher plasma cortisol values had scored higher on HRS. This relationship was seen at all the times on day one (Table 5). It was also that patients who were least severe maintained their suppression of plasma cortisol for complete 24 hours; with increasing severity they showed gradual early escape from suppression with the result that patients who were severe most depressed did not show any suppression at all at 0800 hrs. (Table 6). Patients who showed suppression of urinary 11 OHCS level had a HRS score of 32.75 as compared to 42.0 score seen in 22 patients who did not show suppression.

Discussion

The findings of the present study that 46.6 per cent of depressives could be diagnosed at a confidence level of 93.3 per cent is comparable to other studies where the sensitivity of DST has been shown to vary between 40 per cent to 50 per cent and specificity of about 96 per cent as compared to other psychiatric disorders. Urinary free cortisol after dexamethasone alone was the best indicator of differentiating depressives, as about 73.3 per cent of depressives could be differentiated. Base levels of plasma cortisol though were raised at all the time in depressives, reached significant level only at 2330 hrs. indicating absence of normal hypothalamopituitary adrenal activity inhibition.

The study has also replicated the findings that the abnormality of DST seen in de-

Table 5
Mean plasma corticol level at different times on day one in the 2 categories of severity of depression.

Severity of depression Hamilton rating scale score ranges)	Arithmatic mean plasma cortisol level (μg/100 ml)		Geometric mean plasma cortisol level in μg/100 ml. (S.D. range)
	0800 hours	1600 hours	2330 hours
26–35 N = 13	17.86 ± 5.42	14.19 ± 4.75	7.68 (4.5–30.5)
36–45 N = 6	19.97 ± 3.25	14.18 ± 2.06	9.48 (4.5–11.1)
46–55 N = 9	26.77 ± 4.14	18.87 ± 2.2814	13.10 (7.8–20.6)
56–66 N = 2	36.05 ± 2.06	34.4 ± 1.13	32.56 (31.0–34.2)

Table 6
Number of depressed patients escaping from suppression at different times and their mean scores on Hamilton Rating Scale.

Patients escaping dexamethasone suppression at	No.	Mean HRS Score
0800 hours	3	52.67
1600 hours	8	46.5
2330 hours	4	38.0
Not escaping till 2330 hours	15	33.6

pressives is not that of complete absence of suppression, but rather an early escape from this suppression. Carroll (1982) has also shown that the proportion of abnormal test results detected by the three blood samples was 25 per cent at 0800 hours, 48 per cent at 1600 hours and 71 per cent at 2300 hours.

The results shown indicate a high specificity of changes in DST during attack of depression. The test may be used as an auxillary method for a differential diagnosis between Depression and Schizophrenia. Cortisol values after dexamethasone were better discriminator than before dexamethasone especially urinary 11-OHCS levels. But a normal suppression response will not necessarily exclude the diagnosis of depression in an individual patient. Studies are being conducted wherein an attempt is being made to differentiate suppressors from non-suppressors on the basis of symptoms and response to treatment. One criteria which we could find out was the severity of depression. The question is not settled yet and many more studies are required in this area before the value of a positive DST result could be used for the diagnosis and treatment of a depressed patient. Concurrent assessment of pituitary adrenal activity and neuro-transmitter metabolites in depressed patients can further add to our understanding of the role of these undoubtedly interrelated neuro-physiological phenomena in depressive illness.

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