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POST DEXAMETHASONE PLASMA CORTISOL LEVELS AS INDICATOR OF TRICYCLIC RESPONSE IN MAJOR DEPRESSION

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SUMMARY

Present study suggest that changes in response to the post dexamethasone plasma cortisol levels in the patients of major depression receiveing antidepressents (Imipramine and Amitryptyline) might represent a laboratory marker of clinical progress. We estimated post dexamethasone plasma cortisol levels weekly in thirty hospitalized patients during pre-treatment, post-treatment and drug free post-treatment wash out period. In most of the cases normalization of the post dexamethasone cortisol levels coincided with clinical improvement and failure to normalize was often associated with poorer clinical recovery. No significant difference was observed in the treatment response between imipramine and amitryptyline based on post dexamethasone plasma cortisol levels.

Monitoring treatment progress in psychiatric disorders have been persistent issue to distinguish patients who should respond to somatic treatment from those who are more appropriately managed by other modes of treatment. A number of recent studies have suggested that dexamethasone suppression test (post dexamethasone plasma cortisol level) might serve as an ancillary index to predict clinical response and outcome in patients receiving antidepressent treatment (Carroll, 1972; Dysken et al., 1979; Albala and Greden, 1980; Goldberg, 1980; Papakostas et al., 1980; Holsboer et al., 1982; Turgum et al., 1982).

Brown et al. (1980 & 1981) attempted to understand whether specific thymoleptic drug has preferentially better treatment response in depressed patients with abnormal response to dexamethasone suppression test. He found patients with evidences of hypothalmic-pituitary-adrenal axis hyperactivity as measured by DST responded to imipramine or desimipramine, while those with normal DST responded to amitryptyline or chlorimipramine. However Nelson et al. (1982) failed to find significant difference between imipramine and amitryptyline treatment on DST results.

The present study is an attempt to study the effect of treatment (imipramine and amitryptyline) and clinical response on the post dexamethasone plasma cortisol level (dexamethasone suppression test) and to resolve above controversy.

Material and Methods:

After screening outpatients in the department of psychiatry, King George's Medical College and Gandhi Memorial and Associated Hospitals, Lucknow, 35 patients were selected for present study. After obtaining informed consent they were accepted into this study. Patients were hospitalized if they met following criteria:(1) age between 17 to 60 years (2) fulfilling the Research Diagnostic Criteria of Major Depression (Spitzer et al., 1978) (3) a minimum score of 17 points on the first 17 items of Hamilton Psychiatric Rating Scale for Depression (Hamilton, 1960). They were further classi-

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fied according to International Classification of Diseases Ninth revision (WHO, 1977) into manic depressive psychosis depressed type (296.1) and manic depressive psychosis circular type currently depressed (296.3). Criteria for exclusion in the study were (1) severe physical illness requiring concomitant medication (2) evidences of narrow angle glaucoma, prostatic hypertrophy (3) history of alcoholism, drug intake such as phenytoin sodium, barbiturates, maprobamate, glutothemide, methaqualone, carbamazepine or cyprohiptadine, (4) evidences of endocrinal disorder such as hypopituitarism, Addison's disease (5) evidences of neuropsychiatric illness such as epilepsy, mental retardation and organic brain syndrome, (6) High suicidal risk (7) pregnancy. Complete physical examination was followed by laboratory examination to rule out systemic disorder.

Five patients were dropped from the study due to various reasons. An equal number of age and sex matched control subjects were selected fulfilling the predefined selection criteria.

The patients of experimental group fulfilling the selection criteria were randomly assigned according to random table to group-A (Imipramine) or group B (Amitryptyline) following a drug free observation period of 7 days. The patients of both groups received a fixed doses of 225 mg/day which was achieved within a week starting from 75 mg/day and continued for six weeks provided there were no serious side effects. Subsequent to the completion of treatment, all patients in group A & B were kept free of drugs for a period of 7 days post treatment washout period so as to nullify effect of antidepressant drugs.

Blood for determination of plasma cortisol was obtained on weekly interval at 4 P.M. and 11 P.M. on the day following oral administration of 1 mg of dexamethasone. Coniciding with the weekly measurement of plasma cortisol severity of depression was rated on Hamilton Psychiatric Rating Scale for Depression and plasma cortisol was analysed by the Mattinglay's method (Mattingley, 1962) at Industrial Toxicology Research Centre, Lucknow.

Results:

Sample of the study consists of 30 depressed patients and 30 controls who completed the study and were analysed. The mean plasma cortisol levels (ug/dL) for depressed patients and controls were 18.08 (±5.98) and 11.34 (±2.52) respectively. Mean plasma cortisol level is higher in depressed patients as compared to controls and it is statistically significant ($t=4.81$; d.f.=58; $p<0.001$).

In the imipramine group 9 patients out of 15 showed improvement whereas 6 did not. In amitriptyline group 10 patients out of 15 improved and rest 5 did not show improvement at the end of treatment period.

Imipramine Group:

In the improved patients there was a significant decrease of plasma cortisol levels in post-treatment ($t=3.25$; d.f.=8; $p<0.05$) and post-treatment after washout periods ($t=2.73$; d.f.=8; $p<0.05$) as compared with pretreatment levels. There is some decrease in mean plasma cortisol level at post-treatment period but statistically it was insignificant.

In non-improved patients pre-treatment post-treatment and post-treatment after washout period plasma cortisol levels were 19.58 (±6.62),18.93 (±5.88) and 18.44 (±4.72) respectively. Differences in plasma cortisol levels during these periods were statistically insignificant.

Amitriptyline Group:

In improved patients with amitriptyline treatment like the imipramine, there was significant decrease of mean plasma cortisol

Table-1 Mean Plasma Cortisol levels (μ g/dl) at various stages of treatment with imipramine and amitryptyline

	Pre-treatment (A)		Post-treatment (B)		Post-treatment after washout period (C)		Significance (Paired 't' test)			
	Mean	s.d.	Mean	s.d.	Mean	s.d.	A Vs B	A Vs C	B Vs C	d.f.
Imipramine (N=15)										
Improved (N=9)	17.80	4.52	13.43	4.09	12.09	3.97	3.25	2.73*	1.55	8
Not Improved (N=6)	19.58	6.62	18.93	5.88	18.44	4.72	0.99	0.68	0.34	5
Amitryptyline (N=15)										
Improved (N=10)	17.94	6.32	11.98	3.87	12.55	4.21	3.89**	2.61*	0.81	9
Not Improved (N=5)	17.00	6.38	15.94	5.49	14.88	5.15	0.99	0.34	0.68	4

** – $p < 0.01$, * – $p < 0.05$

Table-2 Mean plasma cortisol levels (μg /dl) in improved and not improved patients at various stages of treatment

	Pre-treatment (A)		Post-treatment (B)		Post-treatment after washout period (C)		Significance (Paired 't' test)			
	Mean	s.d.	Mean	s.d.	Mean	s.d.	A Vs B	A Vs C	B Vs C	d.f.
Improved (N=19)	17.87	5.54	12.67	4.04	12.35	4.07	5.13**	3.86*	0.39	18
Not Improved (N=11)	18.41	6.63	17.57	5.89	18.82	5.48	2.03	1.25	1.88	10

* – $p < 0.01$, ** – $p < 0.001$

levels in post-treatment (t=3.89; d.f.=9; $p < 0.01$) and in post-treatment washout period (t=2.61; d.f.=9; $p < 0.05$) as compared to pre-treatment period.

Decrease in mean plasma cortisol levels in post-treatment after washout period compared to post-treatment level was significant (t=0.81; d.f.=9; N.S.).

Table-2

In the non improved patients mean plasma cortisol levels were 17.00 (±6.38), 15.94 (±5.49) and 14.88 (±5.15) respectively. The difference in plasma cortisol levels during these peroid was insignificant.

In improved patients mean plasma cortisol levels in pre-treatment, post-treatment and post-treatment after washout period were 17.87 (±5.54), 12.67 (±4.04), and 12.35 (±4.07) respectively with a range of 9.20 to 27.80, 7.05 to 20.75 and 7.20 to 22.45 respectively. There is significant decrease of mean plasma cortisol level from pre-treatment to post-treatment (t=5.13; d.f.=13; $p < 0.001$) and post-treatment after washout period (t=3.86; d.f.=18; $p < 0.01$). Fall of mean plasma cortisol in post-treatment after washout period as compared to post-treat ment level was insignificant.

In contrast there were insignificant changes in the mean plasma cortisol levels in pre-treatment, post-treatment and post-treatment after washout period from pre-treatment levels. Mean plasma cortisol in

these periods were 18.41 (±6.63), 17.57 (±5.89) and 18.82 (±5.48) respectively.

Discussion:

In the present study the patients received imipramine or amitriptyline on fixed doses of 225 mg/day which was achieved within a week of starting the treatment and continued for a period of 6 weeks which means that the patients were treated with an adequate doses for adequate period of time. Same period of study has also been taken by Nelson et al. (1982) and Greden et al. (1983). In imipramine treated group (N = 15) 13 patients received treatment for six weeks and the other two showed clinical improvement (HRS-D score less than 10) after five weeks of treatment. Whereas, in the amitriptyline treated group (N = 15) three patients received treatment for five weeks and 12 patients had to be continued for the total study period of six weeks. The response rate in the imipramine treated group was 66% whereas it was 67% in the amitriptyline treated group. Almost similar difference in the response rate of imipramine and amitriptyline group of treated patients had been observed by Cole and Davis in 1975 (70% improvement in imipramine group and 75% in amitriptyline group). However, Sandifer et al. (1965) found no difference after 4 weeks of treatment with imipramine or amitriptyline in depressed patients.

The present study failed to demonstrate differences in the treatment response between imipramine and amitriptyline based on pre-treatment hypothalamic-pituitary-adrenal axis. These findings do not support preliminary report by Browm et al. (1980 and 1981) that dexamethasone suppression test predicted good response to the norepinephrine uptake blocking antidepressants imipramine and desipramine and that dexamethasone suppression predicted better response to the serotonin reuptake blockers, amitriptyline and chlorimipramine. However, it is also known (Mitre et al., 1980) that imipramine and amitriptyline are not pure reuptake blockers of norepinephrine and serotonin respectively. Because of this lack of specificity of the tricyclic antidepressant agent, the findings of present study along with that of Nelson et al. (1982), are likewise not inconsistent with the hypothesis of central noradrenergic inhibition and serotonergic stimulation of hypothalamicadrenal axis (Corticotropin releasing factor-adrenocor-ticotropine-hormone-cortisol pathway).

The mean plasma cortisol levels in improved and not improved patients on either imipramine or amitriptyline treatment were compared at pre-treatment, post-treatment and post-treatment after 7 days washout period respectively. In the improved group the mean plasma cortisol level at pre-treatment phase was significantly decreased after 6 weeks treatment of imipramine or amitriptyline and was equivalent to the mean level plasma cortisol of control subjects. Similar was the case for the mean value of Hamilton Psychiatric Rating Scale for Depression-total score at the end of 6 weeks treatment period. After 7 days post-treatment washout period the mean plasma cortisol level remained more or less unchanged, whereas the mean HRS-D total score increased from 2.63 to 14.84.

However, in the not improved group of patients the mean plasma cortisol level during the pre-treatment phase remained more or less unchanged after 6 weeks treatment of either imipramine or amitriptyline and also after a 7 days post-treatment washout period. Similarly, the HRS-D total scores did not show marked change during these three treatment phases. These findings are in confirmity with that of Brown and Shuay (1980), Paykel and Coppen (1979) and favour the state dependant nature of dexamethasone suppression test on a firm footing.

The present study along with that of Greden et al. (1983), confirm that repeated post dexamethasone plasma cortisol levels

(DST) have applicability for treatment of depressives, that in a number of cases they progressively normalize with clinical improvement, that failure to normalize seems to be often associated with poorer clinical outcome and that repeated testing is safe and well tolerated. A number of potential uses for repeated post dexamethasone plasma cortisol levels stem from the present study and previously reported data. The first situation is common; it occurs when a depressed patient shows clinical improvement during treatment and the post dexamethasone plasma cortisol levels response is simultaneously normalizing. Clinical ratings and dexamethasone suppression test results support each other in this situation, and the test confirms clinical impressions that the psychotropic medication is effective and should be continued. Such laboratory feed back may be valuable in guiding the clinician to continue the treatment. Post dexamethasone plasma cortisol level normalization concomitant with clinical remission indicate that antidepressant treatment can safely be discontinued.

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