Self-Reported Diurnal Mood Changes, Early Morning Awakening and the Dexamethasone Suppression Test in Endogenous Depression

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Summary

Several authors have suggested that Dexamethasone Suppression Test (DST) non-suppression is related to circadian alternations of hypothalamic–pituitary–adrenal function. Two clinical manifestations of altered circadian rhythms in depressed patients are early morning awakening and diurnal variation in mood. To observe whether these clinical symptom patterns were associated with an increased frequency of abnormal DSTs, we examined post-DST plasma cortisol concentrations and matched clinical ratings of early morning awakening and diurnal variation in mood in 49 patients with major depressive disorder, endogenous subtype. We found no significant association between these clinical and laboratory variables.

Introduction

Early morning awakening and diurnal variation of mood are distinctive features of affective disorders (Haider 1968; Mellerup and Rafaelsen 1979; Hamilton 1982; Wehr and Wirz-Justice 1982). Each symptom is currently incorporated into the Research Diagnostic Criteria (Spitzer et al. 1977) and

the DSM-III (American Psychiatric Association 1978) as diagnostic parameters for Major Depressive Disorder, endogenous or melancholic subtype. Each symptom has been linked with the circadian rhythm alterations noted in endogenous depression (Rafaelsen and Mellerup 1977; Stroebel 1981; Wehr and Wirz-Justice 1982). Neuroendocrine abnormalities in circadian patterns in patients with Major Depressive Disorder have been reported for prolactin (Halbreich et al. 1979; Mendelewicz et al. 1980), and ACTH and cortisol (Sachar 1976; Reus et al. 1982), suggesting that the basic limbic physiopathology in affective disorders is related to a desynchronization and phase shifting of 'biological clocks' controlling the circadian rhythms (Mel-

lerup and Rafaelsen 1979; Wehr et al. 1979; Pepper et al. 1983).

The dexamethasone suppression test (DST) has been proposed as a biological correlate for major depressive disorder endogenous subtype (Carroll et al. 1981). Folllowing the 1 mg overnight standardized DST, 30–60% of patients show non-suppression at one or more of three time points, 8:00 am, 4:00 pm, or 11:00 pm (Carroll 1982), depending upon dose of dexamethasone, number of plasma samples, type of cortisol assay and other sources of variance. DST non-suppression is hypothesized to be an expression of limbic–hypothalamic–pituitary–adrenal (LHPA) axis disinhibition. This disinhibition, in turn, has been attributed to altered circadian rhythmicity (Wehr and Wirz-Justice 1982), overriding the inhibitory effects on the dexamethasone.

Most studies dealing with circadian clinical patterns in affective disorders have not assessed simultaneously biological markers. To evaluate possible associations between self-reported diurnal variation of mood, early morning awakening, and DST results in hospitalized patients with endogenous depression, we tested the hypothesis that patients with these two clinical features would show increased DST non-suppression. Our findings failed to support this hypothesis.

Patients and Methods

We studied 49 patients hospitalized in the Clinical Studies Unit of the University of Michigan Psychiatric Hospitals. We evaluated each patient with our standard diagnostic procedure, which includes a clinical interview by one or two faculty psychiatrists, a structured interview using the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott 1975), a diagnostic family interview, a review of past medical records whenever available, and a comprehensive physical examination and laboratory screening to rule out significant medical illness. In order to participate in the study, patients needed: (1) informed consent for participation; (2) a diagnosis of major depressive disorder endogenous subtype by Research Diagnostic Criteria (Spitzer et al. 1977); (3) a DST performed in conjunction with clinical ratings of diurnal variation of mood and early morning awakening; (4) the absence of ex-

clusion criteria for the DST (Carroll et al. 1981); (5) a score of 12 or more in the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), only three subjects had HRSDs of less than 16; (6) self-reported diurnal variation of mood and early morning awakening. Ratings were performed during the first week of hospitalization by clinicians blind to DST results. We used the standardized 1 mg overnight DST, accepting 5 μg/dl as a cutting value for non-suppression using the competitive protein-binding method of Murphy for cortisol assays (Carroll et al. 1981). Patients with any post-dexamethasone cortisol level (from either 8:00 am, 4:00 pm, or 11:00 pm) which exceeded 5 μg/dl were considered non-suppressors.

We rated early morning awakening as present if the patient awakened 1–3 h earlier than usual and was unable to fall asleep again as documented by nurses' observations. We chose this operational definition of early morning awakening to differentiate with middle insomnia. We considered diurnal variation of mood to be present only if the patient reported that mornings were distinctively worse than evenings and ward observations by staff confirmed this complaint. To enhance homogeneity, only patients who definitely had or did not have each of the symptoms were included in the study. Because weight loss has been suggested to invalidate DSTs (Berger et al. 1983; Edelstein et al. 1983), we recorded patients' reports on weight changes throughout the current episode, grouping together those patients with reported losses of 1 kg or more. Most patients were being tapered off their psychotropic medication(s) in preparation for the drug-free period usually in effect in our unit; 15 patients were already drug-free at the moment of testing, 28 patients were receiving antidepressants or antianxiety medications and 6 were on antipsychotics. No medication received is known to affect DST results (Carroll et al. 1981).

Prior to conducting statistical analysis we log transformed plasma cortisol concentrations in order to improve normality of distribution and equality of variance. HRSD scores, age and post-DST cortisol values were analyzed using 2-tailed Student's t-tests. Sex, weight loss, endogenous features and categorical suppressive and non-suppressive status were analyzed using chi-squares with the Yates correction.

TABLE 1

DESCRIPTIVE FEATURES FOR PATIENTS WITH (+) OR WITHOUT (−) DIURNAL VARIATION (DV), EARLY MORNING AWAKENING (EMA) AND BOTH VARIABLES SIMULTANEOUSLY

	DV					EMA					Both				
	n		Mean ± SD		Significance	n		Mean ± SD		Significance	n		Mean ± SD		Significance
	+	−	+	−		+	−	+	−		+	−	+	−	
HRSD[c]	19	30	25.7± 4.9	23.3± 7.5	−1.20[a] NS	23	26	25.4± 5.6	20.9± 6.3	−2.66[a,d]	15	34	24.7± 5	22.3± 6.8	1.21[a] NS
Age (yr)	19	30	53.2±16.2	47.9±13.7	−1.22[a] NS	23	26	53.3±14.2	47.0±14.9	−1.50[a] NS	15	34	53.3±15	48.5±14.6	1.06[a] NS
Sex															
Females	14	25	−	−	0.04[b] NS	17	7	−	−	0.11[b] NS	11	23	−	−	0.004[b] NS
Males	5	10	−	−		6	9	−	−		4	11	−	−	
Endogenous															
Definite	15	25	−	−	0.00[a] NS	18	22	−	−	0.04[a] NS	11	29	−	−	0.36[a] NS
Probable	4	5	−	−		5	4	−	−		4	5	−	−	

[a] Student's t-test.
[b] χ^2 with Yates' correction.
[c] Hamilton Rating Scale for Depression.
[d] $P < 0.05$.

TABLE 2

DST RESULTS AND WEIGHT CHANGES IN PATIENTS WITH (+) OR WITHOUT (−) DIURNAL VARIATION (DV), EARLY MORNING AWAKENING (EMA) AND BOTH VARIABLES SIMULTANEOUSLY

	DV					EMA					Both				
	n		Mean +	SD	Significance	n		Mean +	SD	Significance	n		Mean +	SD	Significance
	+	−	+	−		+	−	+	−		+	−	+	−	
8:00 am DST															
Sup.	11	22	−	−	0.66 [b] NS	15	18	−	−	0.00 [b] NS	10	23	−	−	0.07 [b] NS
Non-Sup.	8	8	−	−		8	8	−	−		5	11	−	−	
Any DST															
Sup.	6	14	−	−	0.08 [b] NS	9	11	−	−	0.05 [b] NS	6	19	−	−	0.01 [b] NS
Non-Sup.	10	16	−	−		12	14	−	−		7	17	−	−	
8:00 am Post-DST Cortisols	19	30	6.85 ± 8.59	5.85 ± 8.16	−0.59 [a] NS	23	26	5.49 ± 7.48	6.46 ± 9.02	0.95 [a] NS	15	34	9.45 ± 9.98	7.80 ± 7.61	0.50 [a] NS
Highest Post-DST Cortisol	16	36	9.53 ± 9.69	8.70 ± 9.26	−0.69 [a] NS	21	25	9.50 ± 9.74	8.55 ± 9.08	0.85 [a] NS	13	33	6.86 ± 9.22	4.85 ± 5.48	0.96 [a] NS
Weight changes															
Loss	10	18	−	−	0.00 [b] NS	10	18	−	−	0.188 [b] NS	7	21	−	−	0.18 [b] NS
None	8	12	−	−		12	8	−	−		7	13	−	−	

[a] Student's t-test.
[b] χ^2 with Yates' correction.
[c] Absolute cortisol values.
[d] Statistics obtained by log transformation.

Results

Demographic features are listed in Table 1. Forty-nine patients, 15 males (age range 21–68, mean 48.26) and 34 females (age range 26–78, mean 46.7), were included in the study. All 49 patients had valid 8:00 am postdexamethasone cortisol samples; only 46 had complete (8:00 am, 4:00 pm, 11:00 pm) post-dexamethasone sampling. Fifty-six percent of the total sample had a non-suppressive DST (31% at 8:00 am, 32% at 4:00 pm, 35% at 11:00 pm).

Nineteen of 49 patients (38%) reported having distinctive diurnal variation of depression. We identified no significant differences in sexual distribution, age, HRSD ratings, or diagnosis of endogenous subtype (definite or probable) between patients with and without diurnal variation (Table 1). Diurnal variation was not associated with higher cortisol values nor increased frequency of abnormal DSTs at any of the post-dexamethasone cortisol samplings (Table 2).

Twenty-three of 49 patients (47%) reported early morning awakening. In this group, the severity of the depression was compared by subtracting the early morning awakening ratings in the HRSD from the total HRSD rating. Patients having distinct early morning awakening were significantly more depressed ($t = -2.66$, $P < 0.01$) than those without it. Other parameters (sexual distribution, age, and definite or probable diagnosis of endogenous subtype) were similar in both groups (Table 1). Even though patients with early morning awakening were significantly more depressed, they showed no differences in their cortisol values and categorical DST responses, neither for the 8:00 am nor for the overall sampling of post-dexamethasone cortisols (Table 2).

Fifteen of 49 patients (31%) reported having diurnal variation and early morning awakening simultaneously. As for the other groups (demographical or cortisol related), no distinctive features were noted for these patients, HRSD ratings did not differentiate between the groups (Tables 1 and 2).

We compared patients reporting weight loss during the episode with those reporting no weight change or weight gain. No significant differences were found between the groups for any of the post-DST plasma cortisol samples (Table 2).

Comments

We were unable to identify any significant association between abnormal diurnal circadian patterns—represented by diurnal variation of mood and early morning awakening—and DST results in this sample of 49 patients with endogenous depression. We had hypothesized that patients with symptoms suggestive of altered circadian regulation would show abnormal DST results more often, presumably due to a phase advancement in cortisol secretion patterns. We failed to find this, however. Brown and Shuey (1980) reached a similar conclusion and reported that patients *without* diurnal variation of mood had a higher frequency of abnormal (2 mg) DST results. Pepper et al. (1983) used a different approach to study possible associations between circadian factors and DST results by alternatively administering 1 mg of dexamethasone at 11:30 pm and 7:00 pm to 6 patients with Major Depressive Disorder. They found similar post-dexamethasone responses in suppressors and non-suppressors at both times of administration of the drug and concluded that DST results were unaffected by changing the hour of administration of the dexamethasone. They stated, as Carroll et al. (1968) had done previously, that phase advancement in cortisol secretion patterns does not seem to play a role in DST non-suppression. Abnormal DSTs have been reported after anticholinergic withdrawal (Greden et al. 1983) particularly after abrupt withdrawal. Even though a significant number of our patients were being tapered from medications with anticholinergic potency, we do not think this affected our results because the sensitivity of the DST in our sample correlates well, and if anything, is slightly lower than that previously reported by our unit (Carroll et al. 1981) and the medications were tapered slowly.

Abnormal clinical circadian patterns are very interesting features of patients with endogenous depression. Our patients reported diurnal variation in mood, early morning awakening and both features simultaneously in 39%, 47% and 31% of the cases respectively. Reported frequencies of diurnal variation in mood can vary from no occurrence at all to being present in almost every patient (for review see Mellerup and Rafaelsen 1979). On the

other hand, early morning awakening is consistently reported in approximately half of the patients with endogenous depression (Rosenthal and Gudeman 1967; Woodruff et al. 1967). As previously stated, we found no significant association between these clinical patterns and the post-dexamethasone plasma cortisol responses. This dissociation may be of relevance to neuroendocrinological research in affective disorders. From the clinical and therapeutic point of view, it would be of great interest to follow these patients throughout the course of their illness and observe whether they constitute a different subgroup of patients, or whether patients showing circadian clinical changes are the ones responsive to therapeutic manipulations—like sleep deprivation—of their chronobiological rhythms.

The diurnal variation of cortisol secretion has been one of the most frequently studied neuroendocrine variables in affective disorder patients. Several abnormalities like circadian hypersecretion, an increased number of secretory episodes, the fluctuating of the circadian secretory curve, the earlier onset (as related to sleeping time) of cortisol secretory episodes and the abnormal response to the DST test have been well established (Sachar 1976; Carroll et al. 1981; Jarrett et al. 1983). These findings suggest significant disturbances of normal phasic relationships between the circadian cortisol secretory pattern, the sleep–wake cycle and diagnosis of affective disorder. Abnormal hypothalamic–pituitary–adrenal (H–P–A) axis function in affective disorders may be secondary to dysfunction of one or more of the several (basal, stress-evoked, circadian and feedback release) (Krieger 1979) mechanisms involved in ACTH release regulation. It may well be that the DST, a measure of feedback release, involves different neuroanatomical pathways and different neurotransmitter systems than the circadian regulation of cortisol secretion; this in turn may explain why abnormal DSTs and circadian alterations in mood and sleep do not correlate. Therefore, we suggest that the study of the H–P–A axis function in affective disorders should involve research procedures and clinical ratings that take into account the different possible abnormal mechanisms involved in cortisol secretion regulation and clinical symptom patterns (like diurnal variation in mood and early morning awakening).

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