
Serial Dexamethasone Suppression Tests in Simultaneous Panic and Depressive Disorders

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Recent work suggests that the simultaneous occurrence of major depressive disorder (MDD) and panic disorder (PD) may be of relevance for clinical findings, therapeutic outcome, and prognosis. It is of interest to know whether or not this relevance extends to biological findings. We addressed this question through comparison of serial Dexamethasone Suppression Test (DST) results in patients who had either MDD alone or simultaneous MDD and PD. We were unable to describe differences between the groups.

Introduction

Recent communications have stressed the frequent association of panic disorder (PD) and major depressive disorder (MDD) (Leckman et al. 1983a,b; Breier et al. 1984; Bueno et al. 1984; Weisman et al. 1984; Grunhaus et al. 1984, 1985, 1986; Grunhaus and Birmaher 1985). It appears that when PD combines with MDD, a more severe disturbance may then be present; these patients may have (1) increased need for psychiatric treatments and hospitalizations, (2) poorer treatment outcome and prognosis, and (3) increased incidence of family psychopathology. It is then important to determine whether or not the combined condition of PD and MDD has biological characteristics that differentiate it from either disorder alone. The Dexamethasone Suppression Test (DST) has been extensively studied in MDD and also in PD or agoraphobia with panic attacks (Curtis et al. 1982; Liberman et al. 1983; Sheehan et al. 1983; Cottraux and Claustrat 1984; Avery et al. 1985; Coryell et al. 1985; Petterson et al. 1985; Roy-Byrne and Uhde 1985). Approximately 50% of MDD patients and less than 20% of PD patients will show DST nonsuppression. Thus, it is of interest to see whether or not the presence of PD in MDD patients has an impact on the suppressibility of the DST when compared to patients with MDD alone. Grunhaus et al. (1984, 1986) and Bueno et al. (1984) have reported on the DST results of patients with MDD and simultaneous PD compared to patients with MDD alone. They found similar rates of nonsuppression in both groups of depressed patients. Grunhaus et al. and Bueno et al. included both inpatients and outpatients in their studies and based their conclusions on a single diagnostic test. To clarify this point further, we studied an inpatient population with simultaneous PD and MDD and compared them to an age- and severity-matched group with MDD alone, using multiple timepoints for the

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DST. The added anxiety diagnosis had no impact on the suppressibility of the DST of the depressed patients. Some interesting clinical features of the combined syndrome were found.

Methods

This study was conducted at the Clinical Studies Unit (CSU) for Affective Disorders, which is a 12-bed inpatient unit with an adjacent outpatient program specializing in research and treatment of affective disorders. We included only inpatients between the ages of 20 and 65 years. Our standard CSU evaluation consisted of a 14-day drug-free period for the majority of patients, several clinical interviews, a structured diagnostic interview [Schedule for Affective Disorders and Schizophrenia (SADS) and SADS-Lifetime Version (SADS-L)], a thorough medical evaluation, and a diagnostic family interview. Comprehensive diagnoses were formulated based on Research Diagnostic Criteria (RDC) (Spitzer et al. 1975).

The study was designed to compare two groups of patients: those with simultaneous PD and MDD (simultaneous group) and those with only MDD (depressed group). The diagnosis of PD was based on the ratings on panic attacks in the current episode of illness obtained from the SADS interview. For inclusion into the simultaneous group, our first step was to determine if subjects met RDC criteria for MDD. Our next step was to determine if subjects met RDC criteria for PD: if so, we diagnosed both conditions regardless of whether subjects had MDD (this is a modification of written RDC criteria for MDD). None of the patients with MDD alone (depressed group) met diagnostic criteria for PD or agoraphobia, either for the current episode of illness or in their life history (as reported in the SADS-L).

The patients in the simultaneous group were matched with patients from the depressed group for the following variables: (1) age within 5 years (2) adjusted Hamilton Rating Scale for Depression (A-HRSD) within 3 points (the A-HRSD was obtained by subtracting the psychic and somatic anxiety ratings), and (3) diagnosis of MDD endogenous subtype and nonendogenous subtype according to RDC. Other inclusion criteria for both groups were: (1) Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) of 12 or more (2) no technical exclusion criteria known to invalidate biological correlates (Carroll et al. 1981), (3) no other illness that could account for the panic attacks, (4) absence of pregnancy, and (5) informed consent for participation in research. Investigators and clinical raters were blind to research variables.

The DST was performed using the standardized version of Carroll et al. (1981), giving 1 mg of dexamethasone at 11:00 PM on day 1 and measuring blood samples at 4:00 and 11:00 PM on day 2. We matched only those who had at least three DSTs during their hospital stay. DSTs were considered nonsuppressive if either of the values of day 2 were above 5 $\mu\text{g}/\text{dl}$. Patients were considered to be nonsuppressors if they had any of the pretreatment DSTs above the cut-off of 5 $\mu\text{g}/\text{dl}$. Plasma cortisol was assayed using a competitive protein-binding assay (Murphy 1967), which has been standardized for the lower ranges of plasma cortisol. The patients with simultaneous MDD and PD reported here are a subsample of those with longitudinal data of a previously reported study (Grunhaus et al. 1986).

Patients were compared on the following variables: (1) HRSD and age-matching criteria; (2) baseline, midtreatment, and predischARGE post-DST plasma cortisol using a cut-off point of 5 and absolute and log-transformed plasma cortisol values; (3) SADS and

SADS-L variables of social function, outcome of previous episode, number of previous episodes of depression, level of function in past 5 years, and Global Assessment Scale (GAS); and (4) a number of clinical variables and family history of affective disorders. Dichotomous variables were analyzed with the chi-square test, matched samples with a paired *t*-test, and unpaired clinical variables with a two-sample Student's *t*-test.

Treatment was prescribed by the attending psychiatrist as clinically indicated. Response to treatment was assessed with our standard method: (1) good response—those having a drop in their HRSD score of 50% or more and having a final HRSD of 10 or less; (2) partial response—whenever the HRSD dropped 50% or more but remained above 10; and (3) poor response—whenever responses 1 or 2 were not met. Treatment regimens were comparable between the groups. Treatment outcome variables will be described in detail elsewhere, as part of a larger sample of treated patients with MDD-PD (Grunhaus et al., in preparation).

Results

Sixteen inpatients with MDD and PD were matched with others with MDD alone. All of the patients were primary MDDs. The matching variables were similar for both groups and are presented in Table 1. As a cross-validation of the adequate matching of the severity of illness, the GAS was also similar in both groups (Table 1). Indicators of hypothalamus-pituitary-adrenal (HPA) function values (highest postdexamethasone plasma cortisol, log-transformed plasma cortisol, and number of nonsuppressors) in the two groups were not significantly different at baseline, midtreatment, or discharge. The process of normalization of the DST with treatment can be observed in Figure 1; the profile analysis at three time points—baseline, midtreatment, and discharge—did not reveal significant differences between the groups.

Table 1. Clinical and DST Variables

	<i>n</i>	MDD-PD ^a	MDD ^b	SD	Paired- <i>t</i>	Two-sample <i>t</i>	χ^2
Age	16	40.5	41.9	2.9	-2.0 NS		
HRSD	16	21.7	19.6	7.3	1.1 NS		
A-HRSD	16	16.7	16.6	5.7	-0.7 NS		
GAS	16	49.4	48.4	17.7	0.2 NS		
D-HRSD ^c	16	9.0	6.5	7.5	0.8 NS		
DA-HRSD ^c	16	7.0	4.9	6.5	0.9 NS		
B-Cortisol ^d	16	5.1 ± 5.1	5.9 ± 7			0.2 NS	
M-Cortisol ^d	16	4.2 ± 1.3	3.8 ± 0.9			0.3 NS	
D-Cortisol ^d	16	4.1 ± 1.8	2.6 ± 0.7			0.8 NS	
Log-DST (base)	16	1.2 ± 0.9	1.1 ± 1.1			1.7 NS	
Percent nonsuppression							
Baseline	16	9/16	8/16				NS
Discharge	16	3/16	3/16				NS
Previous MDD ^e	13/15	2.8 ± 2.9	1.7 ± 1.9		1.2 NS		
Hospitalizations for MDD ^e	12/13	3.6 ± 2.9	1.7 ± 1.9		1.5 0.06		

^aMDD with panic disorder group.

^bMDD only group.

^cD-HRSD, discharge HRSD. DA-HRSD, discharge A-HRSD.

^dB, baseline; M, midtreatment; D, discharge values.

^eNumerator MDD-PD group. denominator MDD only group.

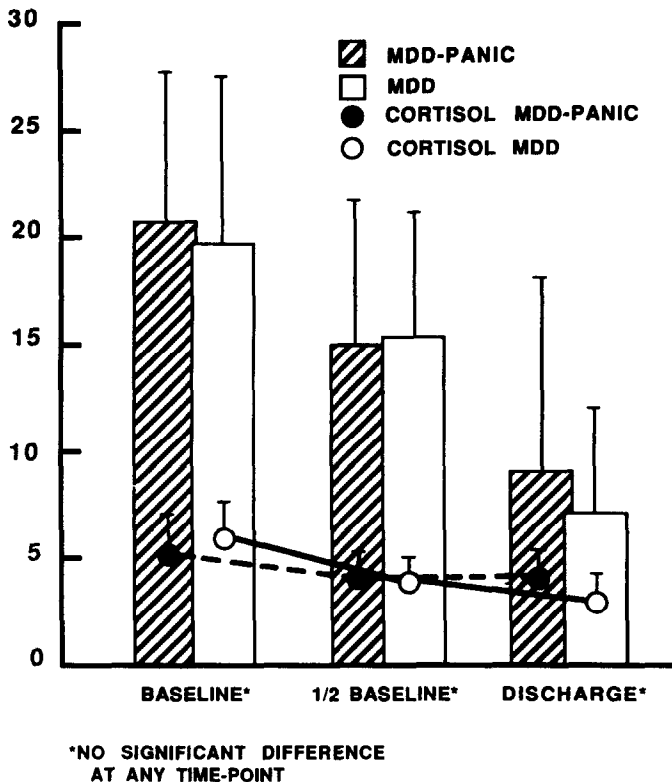


Figure 1. Baseline, midtreatment, and discharge values for the maximal postdexamethasone plasma cortisol values, HRSD, and A-HRSD in patients with MDD-PD or MDD only. Significance measured by paired Student's *t*-tests.

The clinical variables were strikingly similar. The SADS ratings for outcome from previous episodes, highest level of function in past 5 years, social function, and number of outpatient treatments did not differentiate between the groups. A number of longitudinal variables (age at first episode of depression, previous suicide attempts, family history for affective disorders, and length of current episode) were similar in both groups. Interestingly, previous hospitalizations for depression and number of previous episodes of endogenous depression were more frequent, but not significantly different, in those with MDD-PD. The individual HRSD items, including those of psychic and somatic anxiety, did not differentiate between the groups; thus, the patients with PD and MDD were not more severely anxious. The correlations between total HRSD and A-HRSD with baseline postdexamethasone maximal cortisol values were highly significant in both groups (MDD-PD: $r = 0.46$, $p = 0.00001$; MDD: $r = 0.43$, $p = 0.00001$).

Discussion

Our findings confirm previous reports by Grunhaus et al. (1985) and Bueno et al. (1984) that HPA function is not different in MDD and MDD-PD patients. In our population of MDD and PD patients, the rate of nonsuppression (56%) was similar to that of the MDD

only patients (50%). This lack of differentiation persisted throughout the hospitalization and the process of normalization of the DST during treatment. The rate of nonsuppression at discharge was similar in both groups: approximately 20%.

From a clinical perspective, both groups appeared to be very similar. The differences observed were with regard to the number of hospitalizations and previous episodes of MDD. Patients with PD and MDD had been hospitalized more often and also had a history of more frequent episodes of MDD. Even though these results did not reach statistical significance, probably due to the small sample, they may be an indication of a more severe course of illness, which is in line with other recent reports (Breier et al. 1984; Weissman et al. 1984; Leckman et al. 1983a). Further indication of the possibly more severe quality of the combined condition comes from the difficulties these patients have remaining drug-free during our customary diagnostic and observation period. Twenty-five percent of the PD and MDD group could not reach the 2-week drug-free period, whereas all of the MDD only patients were able to do so.

It appears then, that the hypothalamic-pituitary-adrenal (HPA) axis dysfunction, as measured through negative feedback loops with the DST, is very similar in MDD only patients and those with the simultaneous syndrome. Together with the findings of low nonsuppression rates in PD only patients, it is possible to suggest that the underlying physiopathology of PD does not have an impact on the HPA axis function as measured with the DST. These findings support the specificity of the DST with regard to anxiety conditions and, particularly, PD.

Increased levels of adrenergic secretions (epinephrine, norepinephrine, MHPG, and DOPEG) in MDD patients who also have DST nonsuppression have been described by some authors (Barnes et al. 1983; Jimmerson et al. 1983), but not by others (Loo et al. 1985). Similarly, increased adrenergic tone has been proposed as central to anxiety conditions (Redmond and Huang 1979), and some authors have found elevated adrenergic products in panic conditions (Ko et al. 1983; Cameron et al. 1984). It is then possible to suggest that in the presence of both psychopathologies, MDD and PA, the rate of nonsuppression would be higher. As evidenced by our results, we found no difference in the rates of DST nonsuppression in our group of patients.

Even though it appears that the DST results are similar in patients with either MDD or simultaneous MDD and PA, both at pretreatment and discharge time points, it is yet unclear whether or not any differences may be identified in prognosis. In follow-up studies, it would be of interest to test the hypothesis that the simultaneous syndrome of MDD and PA, and by inference to DST nonsuppression associated to a hyperadrenergic state, will have a worse outcome than MDD alone. As mentioned in our introduction, some outcome studies (Van Valkenburg et al. 1984) already lend support to the clinical aspects of this hypothesis. We are currently engaged in a study collecting data to test the biological aspects of it.

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