

Vale W, Spiess J, Rivier C, Rivier J (1981): Characterization of a 41-residue ovine hypothalamic peptide that stimulates the secretion of corticotropin and β -endorphin. *Science* 213:1394-1397.

Valentino RJ, Foote SL, Aston-Jones G (1983): Corticotropin releasing factor activates noradrenergic neurons of the locus coeruleus. *Brain Res* 270:363-367.

The Dexamethasone Suppression Test in Inpatients with Panic Disorder or Agoraphobia with Panic Attacks

Leon Grunhaus, Dolores Tiongco, Roger F. Haskett, and John F. Greden

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis has been meticulously investigated in psychiatric illness, particularly in depression (Sachar et al. 1973; Sachar 1975). The Dexamethasone Suppression Test (DST) as a measure of the integrity of inhibitory feedback loops (Carroll et al. 1981; Stokes et al. 1984; Arana et al. 1985) of the HPA axis has received much attention. Though some controversy remains (Arana et al. 1985), there appears to be a general consensus that moderate to severe major depressive disorder (MDD), particularly in older inpatients, will lead to disinhibition of the HPA axis in a significant number of patients. On the other hand, the DST in patients with panic attacks (PA)—panic disorder (PD) and agoraphobia—has consistently yielded suppression in a

vast majority (82%–100%) of cases (Lieberman et al. 1983; Sheehan et al. 1983; Cottraus and Claustrat 1984; Avery et al. 1985; Coryell et al. 1985; Petterson et al. 1985; Roy-Byrne and Uhde 1985). These results have been interpreted by some authors (Sheehan et al. 1983) as evidence of a biological difference in HPA activity between patients with MDD and patients with PD and agoraphobia. This hypothesis, however, has not been tested in inpatients with PD or agoraphobia. To assess HPA function among inpatients with PD or agoraphobia with PA, we completed a DST during each week of hospitalization; six of the eight patients showed non-suppression at least once during the pretreatment phase of their hospitalization.

Methods

Patients were hospitalized in the Clinical Studies Unit (CSU) of the University of Michigan. Our standard evaluation (Carroll et al. 1981) consists of a 14-day evaluation period, several clinical, family, and structured diagnostic interviews [Schedule of Affective Disorders and Schizo-

From the Department of Psychiatry, Clinical Studies Unit, University of Michigan, Ann Arbor, MI.

Address reprint requests to Dr. Leon Grunhaus, Department of Psychiatry, Clinical Studies Unit, University of Michigan, 1500 E. Medical Center Drive, D9702 Box 0018, Ann Arbor, MI 48109-0118.

Received July 14, 1986; revised September 8, 1986.

phrenia (SADS) and SADS-Lifetime version (SADS-L)], and a thorough physical evaluation. Comprehensive diagnoses follow the Research Diagnostic Criteria (RDC) (Spitzer et al. 1975).

A search in our inpatient records identified eight patients, four women and four men aged 22-58 years, meeting RDC diagnosis of PD or agoraphobia with PA during the current episode of illness. As stated in the RDC criteria, patients can meet these diagnoses only in the absence of an affective diagnosis.

DST and clinical ratings were performed weekly by clinicians blind to laboratory data. The 17-point Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) was the main rating instrument; we also looked at the HRSD with the psychic and somatic anxiety ratings extracted (the A-HRSD). Criteria for exclusion from the study were those recommended by Carroll et al. (1981), Stokes et al. (1984), and Arana et al. (1985). Informed consent for participation in research was required.

The 1-mg DST was conducted at least 3 days after admission, using the procedure of Carroll et al. (1981). DSTs were considered to be nonsuppressive if either value (4:00 PM or 11:00 PM) on day 2 was above 5 $\mu\text{g}/\text{dl}$. Patients were considered to be nonsuppressors if any pretreatment DST exceeded the cut-point of 5 $\mu\text{g}/\text{dl}$. Plasma cortisol was assayed using a competitive protein-binding assay (Murphy 1967), which was standardized for the lower ranges of plasma cortisol.

Results

Figure 1 presents a compilation of the results of the serial measurements of HRSD, A-HRSD, and postdexamethasone plasma cortisols. Six patients showed at least one nonsuppressive DST during the first 2 weeks of hospitalization. Only one patient had a clear history of depressive episodes; interestingly, he was one of the consistent suppressors. There was no significant correlation between HRSD ratings and cortisol values ($r = 0.06$; NS). All but one (patient 1A) of the patients were drug-free for at least 1 week before treatment was started.

Response to treatment varied considerably. Patient 1A received 7 mg/day of alprazolam with poor results. Five patients (2A, 3A, 4A, 6A, and 7A) received imipramine, either alone or in combination with alprazolam. Three of these (3A, 6A, and 7A) showed a good therapeutic response, whereas two could only tolerate 75 mg of imipramine and showed a poor response to treatment. One patient (5A) received phenelzine, 45 mg/day; even though his discharge HRSD was high, a 3-month follow-up showed complete remission of his PA and agoraphobic behavior. The remaining patient (8A) presented only phobic symptoms during hospitalization.

Discussion

Six of eight cases reported showed nonsuppressive DSTs, suggesting that agoraphobia and PD inpatients have nonsuppressive DSTs more often than their outpatient counterparts. This inpatient/outpatient difference, even though tentative because of the small sample studied, raises some interesting questions.

The majority of patients with PA, even those with severe symptoms, seldom require hospitalization. There is fairly good evidence to suggest that whenever hospitalization is necessary, the association with depression is high (Bowen and Kohut 1979; Dealy et al. 1981). The relationship between PA and MDD is further strengthened by recent findings of frequent family history of affective disorder in patients with PD and agoraphobia with PA (Bowen and Kohut 1979; Munjack and Moss 1981; Leckman et al. 1983). Moreover, 60%-70% of patients with these anxiety diagnoses are currently or eventually diagnosed as having MDD as well (Breier et al. 1984).

It is possible, then, that these inpatients with PA are showing the HPA abnormality that is characteristic of endogenous depression, even though they lack sufficient clinical features to justify diagnosis of this condition. It may well be that these patients should be considered as having an affective illness and be treated accordingly. In another study (Grunhaus et al. 1986), we found the rates of DST nonsuppres-

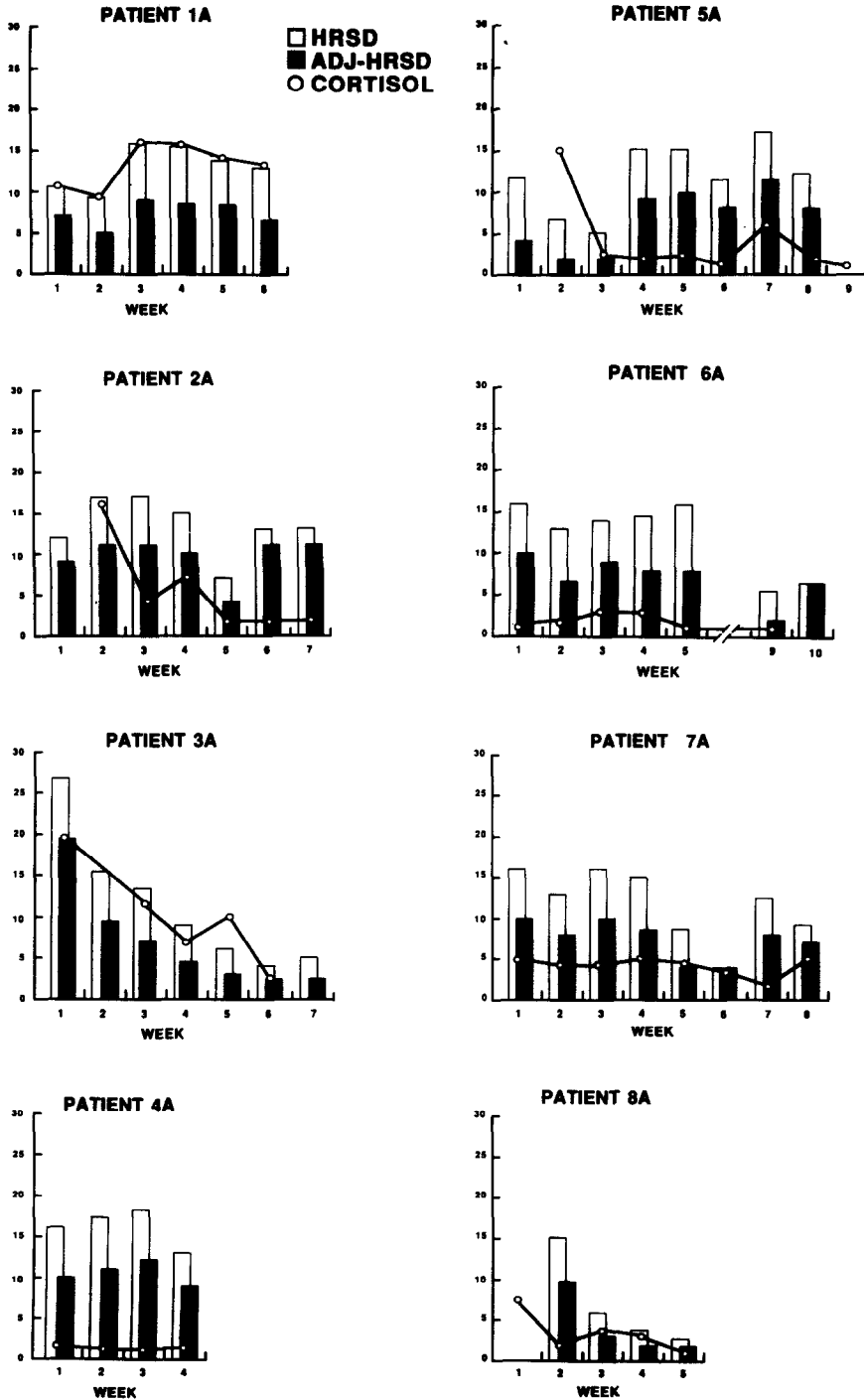


Figure 1. Highest postdexamethasone plasma cortisol, Hamilton Depression ratings (HRSD), and adjusted HRSD ratio (A-HRSD) ratings in inpatients with panic disorder or agoraphobia with panic attacks.

sion to be similar in patients with MDD and MDD with simultaneous PA. Thus, when a specific diagnosis of depression is associated with PA, HPA dysregulation resembles that occurring in depression. The need for hospitalization in patients with PA may be an indicator of a more severe form of illness, probably affective related, that is associated with DST nonsuppression. Support for this hypothesis comes from a report of DST results in primary obsessive-compulsive patients (Insel et al. 1982). Insel et al. found DST nonsuppression in 6 of 16 patients with obsessive-compulsive disorder; all of the nonsuppressors were inpatients and had significant ratings for depression, even though none of them had depression as a primary diagnosis. It may be, then, that HPA dysfunction is a common feature of severe forms of psychiatric illness characterized by either primary or secondary affective pathology.

Supported in part by NIMH Grant 1-RO1-MHM0216-01 and the Psychiatry Department of the University of Michigan.

References

- Arana GW, Baldessarini RJ, Ornstein M (1985): The Dexamethasone Suppression Test for diagnosis and prognosis in psychiatry. *Arch Gen Psychiatry* 42:1193-1204.
- Avery DH, Osgood TB, Ishiki DM, Wilson LG, Kenny M, Dunner DL (1985): The DST in psychiatric outpatients with generalized anxiety disorder, panic disorder or primary affective disorder. *Am J Psychiatry* 142:844-848.
- Bowen RC, Kohut J (1979): The relationship between agoraphobia and primary affective disorders. *Can J Psychiatry* 24:317-321.
- Breier A, Charney DS, Heninger GR (1984): Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41:1129-1135.
- Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol A, Lohr N, Steiner M, de Vigne JP, Young E (1981): A specific diagnostic test for the diagnosis of melancholia: Standardization, validation and clinical utility. *Arch Gen Psychiatry* 38:15-22.
- Clancy J, Noyes R, Hoenk PR, Slymen DJ (1978): Secondary depression in anxiety neurosis. *J Nerv Ment Dis* 166:846-850.
- Coryell W, Noyes R, Clancy J, Crowe R, Chaudhry D (1985): Abnormal escape from dexamethasone suppression in agoraphobia with panic attacks. *Psychiatry Res* 15:301-311.
- Cottraux J, Claustrat B (1984): Le test a la dexamethasone dans l'agoraphobie avec attacks de panique. *Encephale* 10:267-272.
- Curtis GC, Cameron OG, Nesse RM (1982): The Dexamethasone Suppression Test in panic disorder and agoraphobia. *Am J Psychiatry* 139:1043-1046.
- Dealy RS, Ishiki DM, Avery DH, Wilson LG, Dunner DL (1981): Secondary depression in anxiety disorders. *Compr Psychiatry* 22:612-618.
- Hamilton M (1960): A Rating Scale for Depression. *J Neurol Neurosurg Psychiatry* 23:56-62.
- Insel TR, Kalin NH, Guttmacher LB, Cohen RM, Murphy DL (1982): The Dexamethasone Suppression Test in patients with primary obsessive-compulsive disorder. *Psychiatry Res* 6:153-160.
- Leckman JF, Weissman MM, Merikangas KR, Pauls DL, Prusoff BA (1983): Panic disorder and major depression. *Arch Gen Psychiatry* 40:1055-1060.
- Liberman JA, Brenner R, Coccaro E, Borenstein M, Kane JM (1983): Dexamethasone Suppression Tests in patients with panic disorder. *Am J Psychiatry* 140:917-919.
- Munjack DJ, Moss HB (1981): Affective disorder and alcoholism in families of agoraphobics. *Arch Gen Psychiatry* 38:869-871.
- Murphy BEP (1967): Some studies of the protein-binding of steroids and their application to the routine micro and ultra-micro measurements of various steroids in body fluids by competitive protein-binding radioassay. *J Clin Endocrinol Metab* 27:973-990.
- Peterson GA, Ballenger JC, Cox DP, Hucek A, Lydiard RC, Laraia MT, Trockman C (1985): The Dexamethasone Suppression Test in agoraphobia. *J Clin Psychopharmacol* 5:100-102.
- Roy-Byrne PP, Uhde TW (1985): Panic disorder and major depression: Biological relationships. *Psychopharmacol Bull* 21:551-554.
- Sachar EJ (1975): Neuroendocrine abnormalities in depressive illness. In Sachar EJ (ed), *Topics of Psychoendocrinology*. Orlando, FL: Grune & Stratton.

- Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF (1973): Disrupted 24-hour pattern of cortisol secretion in psychotic depression. *Arch Gen Psychiatry* 28:19-24.
- Sheehan DV, Claycomb JB, Surman OS, Baer L, Coleman J, Gelles L (1983): Panic attacks and the dexamethasone suppression test. *Am J Psychiatry* 140:1063-1064.
- Spitzer RL, Endicott J, Robins E (1975): *Research Diagnostic Criteria*. New York: New York Psychiatric Institute, Biometrics Research.
- Stokes PE, Stoll PM, Koslow SH, Maas JW, Davis JM, Swann AC, Robins E (1984): Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. *Arch Gen Psychiatry* 41:257-267.