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Neuroendocrine Aspects of Primary Endogenous Depression: IX. Receiver Operating Characteristic Analysis of the Dexamethasone Suppression Index vs. the Dexamethasone Suppression Test in Patients and Controls

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Abstract. The dexamethasone suppression index (DSI), which is the product of the postdexamethasone (DEX) serum DEX concentration and the post-DEX serum cortisol concentration, has been suggested to be a more sensitive discriminative test for depression than the standard DEX suppression test (DST). We used receiver operating characteristic (ROC) analysis to examine the DSI, calculated in several ways, versus the standard DST in a sample of 40 endogenous major depressives and 40 matched normal control subjects. The ROC analysis indicated that the DSI offers no advantage over the standard DST, regardless of which criterion values are used to define cortisol nonsuppression. Serum DEX determinations appear to have value primarily as an indicator of the minimum DEX concentration necessary for an accurate DST.

Key Words. Dexamethasone suppression index, dexamethasone suppression test, affective disorder, receiver operating characteristic analysis, cortisol.

The dexamethasone (DEX) suppression test (DST) has been studied extensively as one measure of the overactivity of the hypothalamic-pituitary-adrenal (HPA) cortical axis that occurs in 30-50% of patients with major depression (Carroll et al., 1981; Rubin and Poland, 1984; Arana et al., 1985; APA Task Force, 1987; Rubin et al., 1987). One source of the variability in the interpretation of post-DEX serum cortisol values in the DST may be a corresponding variability in serum DEX concentrations (Arana et al., 1984; Holsboer et al., 1984; Johnson et al., 1984; Berger et al., 1985; Lowy and Meltzer, 1987; Maguire et al., 1987; Poland et al., 1987; Carson et al., 1988; Asnis et al., 1989). In an attempt to control for the variability in serum DEX and thereby possibly enhance the performance of the DST, investigators have suggested that expressing the post-DEX serum cortisol value as a function of the serum DEX concentration, the "DEX suppression index" or DSI, can improve

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the discriminative ability of the DST by controlling for the effects of both high and low serum DEX concentrations (Carr et al., 1986; Arana et al., 1988).

Carr et al. (1986) found that cortisol multiplied by DEX^x for each subject at each sampling time, with the exponent x determined from the observed curvilinear relationship between serum cortisol and DEX at each time, produced a modest increase in DST specificity. Arana et al. (1988) reported that the simple product of the serum cortisol value and its corresponding serum DEX value also improved diagnostic performance. However, the comparison of the DSI and the DST in both reports was based on a small number of criterion values used to define non-suppression. We and others have found receiver operating characteristic (ROC) analysis to be a useful technique for comparing and maximizing DST quality and performance that is independent of the biases inherent in arbitrarily chosen criterion values (Kraemer, 1987; McCracken et al., 1988; Mossman and Somoza, 1989*a*, 1989*b*). Reanalysis of the Carr et al. (1986) data by the ROC method indicated that the incorporation of DEX values did not enhance DST performance (Mossman and Somoza, 1989*a*), but this comparison was limited because only data from the 0800h time point were used. Because DEX concentrations influence post-DEX cortisol values less at 0800h than at 1600h or 2300h (see Poland et al., 1987, for references), the 0800h comparison would be least likely to show enhancement by incorporating DEX values.

The purpose of the present report is to provide a more definitive comparison of the DSI and the standard DST through the use of ROC analysis at 8, 16, and 24 hours post-DEX in a sample of 40 primary endogenous major depressives and 40 matched normal control subjects. Cortisol secretory dynamics, serum DEX concentrations in relation to the DST, and an ROC comparison of the cortisol suppression index to the DST in these subjects have been presented previously (Rubin et al., 1987; Poland et al., 1987; McCracken et al., 1988).

Methods

Details of subject recruitment and demographics have been presented earlier (Rubin et al., 1987). Forty depressed patients, ranging in age from 22 to 71 years, were studied. All patients met Research Diagnostic Criteria (Spitzer et al., 1978) for primary, definite endogenous depression on the basis of a structured interview (Schedule for Affective Disorders and Schizophrenia; Endicott and Spitzer, 1978). All patients had a total score of 17 or greater on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The mean HRSD score for the depressed patients was 27 (21-item version). Forty normal control subjects, individually matched to each patient by age, sex, race, and menstrual status for the women, also were studied. Normal controls were screened to rule out any personal history of major psychiatric illness by clinical interview with a research psychiatrist.

Of the 40 patients, 16 were men (median age 39.5 years) and 24 were women (median age 38.5 years). Twenty-three of the 40 patients were inpatients; the remaining 17 were outpatients. All patients and their matched controls were not on medications that might interfere with the endocrine testing. The few patients who had been receiving psychotropic medication before the study underwent a minimum of a 2- or 3-week drug washout period under supervision before study entry.

The protocol for the neuroendocrine testing has been described previously (Rubin et al., 1987). All subjects underwent half-hourly blood sampling during the pre-DEX day via an indwelling venous catheter. Subjects then received DEX elixir (Decadron; Merck, Sharpe and

Table 1. Medians and first and third quartiles for postdexamethasone serum cortisol and dexamethasone (DEX) concentrations (ng/ml) and dexamethasone suppression indexes (DSI) ($nmol^2/l^2$), calculated by 3 methods, for 40 primary endogenous depressives and 40 matched normal controls

		Major depressives		Controls	
Method	Time	Median	1st-3rd Quartiles	Median	1st-3rd Quartiles
Post-DEX cortisol	0700	12.0	9-25	9.0	5-15
	1500	11.5	7-57	8.5	4.5-13.5
	2300	15.0	8-35	9.5	4-13
DEX level	0700	2.7	2.1-3.9	3.4	2.4-4.6
	1500	0.8	0.6-1.2	1.0	0.6-1.5
	2300	0.2	0.2-0.3	0.3	0.2-0.6
DSI #1[1]	0700	280	162-431	194	107-430
	1500	81	48-193	63	25-101
	2300	21	11-47	17	9-39
DSI #2[2]	0700	188	113-274	127	70-254
	1500	51	27-205	39	20-67
	2300	33	17-62	18	12-33
DSI #3[3]	0700	71	47-123	50	29-92
	1500	52	28-209	39	20-68
	2300	33	16-58	18	12-35

1. Method of Arana et al. (1988).
2. Using exponents of Carr et al. (1986).
3. Exponents calculated from our data according to method of Carr et al. (1986).

Dohme) (1.0 mg orally) at 2300h, after which the catheter was removed. On the following day, three blood samples were obtained at 0700h, 1500h, and 2300h. Serum samples were analyzed for cortisol and DEX by specific radioimmunoassays, described previously (Poland and Rubin, 1982; Rubin et al., 1987; Poland et al., 1987).

The DSI was calculated for each subject in three ways. First, according to the method of Arana et al. (1988), the post-DEX serum cortisol concentration was multiplied by the serum DEX concentration at the corresponding time point (e.g., 1500h cortisol value times 1500h DEX value). This is referred to as DSI #1. Second, according to the method of Carr et al. (1986), the serum cortisol concentration was multiplied by DEX^x for each subject at each sampling time. The values of x used were 0.79, 0.50, and 0.43 for 0800h, 1500h, and 2300h, respectively, as determined by Carr et al. from the curvilinear relationship of serum cortisol to serum DEX at each time. This is referred to as DSI #2. Finally, following the method of Carr et al., we determined our own x values at the three times, based on our observed serum cortisol and DEX concentrations. The x values derived by the function $[\text{cortisol}] = b[\text{DEX}]^x$ were 0.33, 0.52, and 0.49 for 0800h, 1500h, and 2300h, respectively. This is referred to as DSI #3.

ROC curves were generated by calculating the sensitivity (proportion of depressives with a positive test) and specificity (proportion of controls with a negative test) for the DSI and DST at each of the three sampling times over a broad range of criterion values, below and above which there were at least 10 patients with a positive or negative test (Kraemer, 1987). For post-DEX cortisol, the criterion values ranged from 6.0 to 50.0 ng/ml for the three time points. For the DSI, the criterion values differed somewhat, according to the method of calculation and the time point examined. ROC curves were generated by plotting sensitivity (% true positive rate) versus 1-specificity (% false positive rate) (Murphy et al., 1987) for the range of criterion values. The background of ROC analysis and statistical properties of ROC

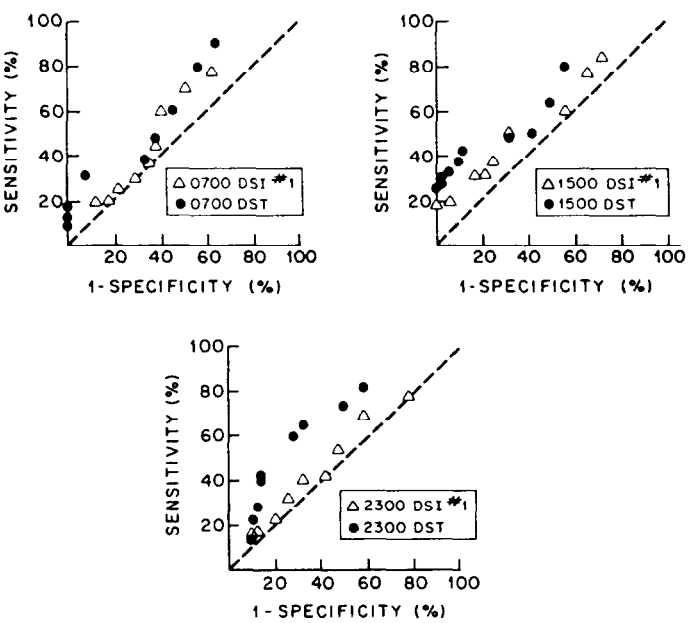
curves have been described elsewhere (Metz, 1978; Swets et al., 1979; Hanley and McNeil, 1982, 1983).

Results

The medians and first and third quartiles for the raw post-DEX cortisol and DEX concentrations and for the three DSIs in the patients and controls at all time points are shown in Table 1. The distributions of the three DSIs were all highly skewed. The ROC curves were compared by visual inspection of the plots (Habicht, 1980; Kraemer, 1987), instead of comparing the area under the curve (Hanley and McNeil, 1982). The comparison of DSI #1 to the standard DST at the three times is shown in Fig. 1. As indicated by the ROC curves, there is a predictable, consistent effect on sensitivity and specificity for both the DSI and the DST as the criterion values change. In ROC analysis, superior test performance is defined as the curve that demonstrates the highest sensitivity (ordinate) at a given value of 1-specificity (abscissa) (Murphy et al., 1987). The curves formed by the highest individual points are similar, although the range of criterion values differs for each. None of the DSI curves fall above the corresponding DST curve; thus, DSI #1 does not have a better test performance.

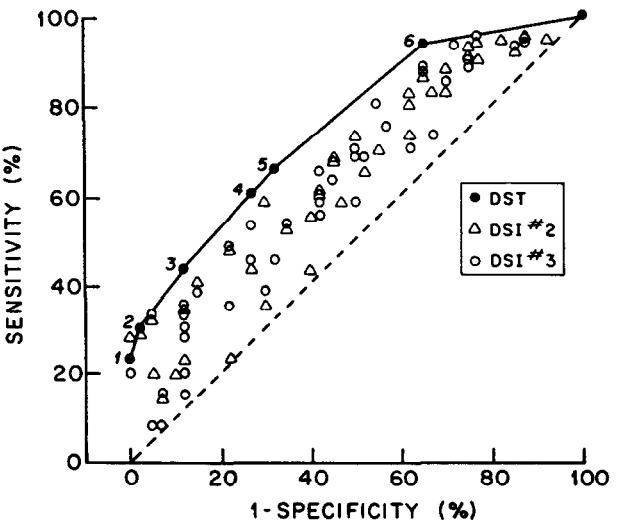
In addition to the separate ROC curves at each time for DSI #1, a composite ROC curve (Kraemer, 1987) was constructed from the DSI #2, DSI #3, and DST data at

Fig. 1. Receiver operating characteristic curves for DSI #1 vs. the DST for 40 endogenous depressives and 40 matched normal controls at 8, 16, and 24 hours post-DEX



DSI = dexamethasone suppression index. DST = dexamethasone suppression test. DEX = dexamethasone.

Fig. 2. Composite receiver operating characteristic curve for all three sampling times, formed by connecting points on the "upper convex hull," which demonstrates the superiority of the DST over DSI #2 and DSI #3.



DSI = dexamethasone suppression index. DST = dexamethasone suppression test. DEX = dexamethasone.

1—0700h DST, criterion of 25 ng/ml; 2—1500h DST, criterion of 40 ng/ml; 3—1500h DST, criterion of 15 ng/ml; 4—2300h DST, criterion of 12 ng/ml; 5—2300h DST, criterion of 10 ng/ml; 6/0700h DST, criterion of 6 ng/ml. Closed circles = DST, open triangles = DSI #2, open circles = DSI #3.

the three times to compare the other DSI calculation methods and to delineate the optimal test references (Fig. 2). Only one DSI point falls slightly above the ROC curve defined by the six optimal DST values. Therefore, in our sample of depressives and controls, there is clear superiority of the DST over the DSI as the more sensitive and specific test, regardless of the method of calculation.

Discussion

Several studies have documented the influence of serum DEX concentrations on the performance of the standard DST in depressed patients (Arana et al., 1984; Holsboer et al., 1984; Berger et al., 1985; Poland et al., 1987; Maguire et al., 1987). This has led some investigators to transform post-DEX serum cortisol concentrations to reflect the corresponding serum DEX concentrations, referred to as the DEX suppression index (DSI) (Carr et al., 1986; Arana et al., 1988). Both studies claimed the DSI to be superior to the DST, but their comparisons were limited by a small number of arbitrarily chosen criterion values. ROC analysis is free of the biases inherent in such arbitrarily chosen criterion values (Kraemer, 1987; Murphy et al., 1987). As mentioned, a limited reexamination of the Carr et al. (1986) data by ROC analysis indicated that the DSI had no advantage over the DST as a discriminative test (Mossman and Somoza, 1989*a*).

Our comparison by ROC analysis of the DSI, calculated three ways, to the standard DST at three times in 40 primary endogenous depressives and 40 individu-

ally matched normal control subjects revealed no advantage in sensitivity or specificity of any of the DSIs over the DST. In a strict sense, our results are valid only for the clinical context of endogenous depressives compared to normal controls. However, because of the often greater frequency of positive DSTs in nondepressed psychiatric patients than in normal subjects, it appears unlikely that a comparison of the DSI to the DST in depressives versus other psychiatric patients would reveal any advantage of the DSI. Thus, further studies of the DST in depression would appear to be best served by continuing to use post-DEX cortisol values as the primary outcome variable, as we also concluded for the cortisol suppression index (McCracken et al., 1988).

The question remains of how best to control for variations in DEX bioavailability in the DST. The range of serum DEX concentrations following oral DEX administration has been well described (Meikle, 1982; Arana et al., 1984; Holsboer et al., 1984; Berger et al., 1985; Maguire et al., 1987; Poland et al., 1987). The influence of the DEX concentration on the cortisol concentration appears to be most prominent for samples 16 and 24 hours post-DEX (Poland et al., 1987); therefore, one approach to attempt to circumvent DEX bioavailability differences would be to focus only on serum cortisol values approximately 8 hours after DEX administration (Poland et al., 1985). Other investigators have suggested that a minimum serum DEX concentration or a serum DEX "window" be achieved for the DST to be considered valid (Meikle, 1982; O'Sullivan et al., 1989). These approaches may prove to be useful in refining the performance of the DST.

Finally, our data again support the ease and usefulness of ROC analysis as a means of comparing test performance. We recommend wider adoption of ROC analysis in future studies of biological tests in psychiatry.

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