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Use of Saliva Cortisol in the Dexamethasone Suppression Test

Marc Ansseau, José Sulon, Adrienne Doumont, Jean-Luc Cerfontaine, Jean-Jacques Legros, Jean-Claude Sodoyez, and Emilie Demey-Ponsart

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Abstract. In a sample of 26 inpatients (15 primary endogenous depressives and a heterogeneous comparison group of 11 psychiatric patients), results of the dexamethasone suppression test (DST) for endogenous depression were compared when cortisol was measured in plasma (total and free) and in saliva. Results showed a close linear relationship among plasma total and free cortisol, plasma total cortisol, and saliva cortisol, and between free plasma and saliva cortisol. A saliva cortisol cutoff point of 70 ng/dl achieved the same sensitivity (67%), specificity (91%), and diagnostic confidence (91%) as the best cutoff scores of plasma total cortisol (5 μg/dl) and plasma free cortisol (0.15 μg/dl). These results suggest that saliva cortisol, which directly reflects the biologically active fraction of cortisol, can be used as a reliable and more practical index in the DST, especially in outpatients.

Key Words. Dexamethasone suppression test, saliva cortisol, free cortisol, endogenous depression.

The overnight dexamethasone suppression test (DST) currently represents one of the most widely used biological markers of endogenous depression, both for inpatients and outpatients (for review, see Carroll, 1982*b*). About 50% of endogenous depressives exhibit an abnormal "escape" from dexamethasone suppression; however, the specificity of this phenomenon in endogenous depression has been a subject of recent controversies (for review, see Hirschfeld et al., 1983). The DST procedure has been standardized: oral intake of dexamethasone, 1 mg, at 11 p.m. on day 1 and measurement of cortisol plasma levels at 4 p.m. and 11 p.m. on day 2. Nonsuppression is defined as a cortisol level higher than 5 μg/dl in either sample (Carroll et al., 1981).

We recently suggested that levels of free (unbound) cortisol, the biologically active fraction of cortisol, could also be used as a reliable index of nonsuppression, with a cutoff limit of 0.10 or 0.15 μg/dl, depending upon desired level of sensitivity and specificity (Ansseau et al., in press). The use of such cutoff limits resulted in an equivalent or sometimes better sensitivity (54-66%) than total cortisol levels (54%), without sacrifice of specificity (81%).

Marc Ansseau, M.D., Adrienne Doumont, M.D., and Jean-Luc Cerfontaine, M.D., are in the Unité de Psychopharmacologie, Hôpital Universitaire de Bavière, B-4020 Liège, Belgium. José Sulon, Ph.D., Jean-Claude Sodoyez, M.D., Ph.D., and Emilie Demey-Ponsart, Ph.D., are in the Département de Clinique et de Pathologie Médicales (Professor H. Van Cauwenberge), Hôpital Universitaire de Bavière, B-4020 Liège, Belgium. Jean-Jacques Legros, M.D., Ph.D., is in the Unité de Psychoneuroendocrinologie, CHU B23, B-4000, Sart-Tilman, Belgium. (Reprint requests to Dr. M. Ansseau.)

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Saliva cortisol, which is directly correlated with plasma free cortisol (Katz and Shannon, 1969), is very sensitive to exogenous stimulation by adrenocorticotropic hormone (ACTH) or inhibition by dexamethasone (Walker et al., 1978; Stahl and Dörner, 1982). Compared to venipuncture, collection of saliva is more practical and stress-free. Since cortisol levels in parotid fluid and mixed whole saliva are in good agreement (Walker et al., 1978), the determinations can be carried out on mixed whole saliva that is easily collected. Preliminary data from Poland and Rubin (1982) showed that six subjects, nonsuppressors after DST, also had saliva cortisol concentrations that were significantly higher than those of suppressors.

The purpose of this study was to test the possible use of saliva cortisol levels in the DST for the diagnostic confirmation of endogenous depression, to determine the best cutoff limit, and to compare the obtained sensitivity and specificity with those produced by plasma total and free cortisol in the same patients.

Methods

Subjects. The study was performed in 26 inpatients representing consecutive admissions to the Psychopharmacology Unit of the University Hospital of Liège, Belgium, and ranging in age from 18 to 66 (mean = 42.3 ± 12.6) years. All diagnoses were made according to Research Diagnostic Criteria (Spitzer et al., 1978) by two independent research psychiatrists using a locally developed semistructured interview and without knowledge of laboratory results. The sample (12 males and 3 females; age range 18-66 years; mean 44.1 ± 12.8 years) was composed of 15 primary major depressives, who met criteria for definite endogenous subtype and had a score of at least 20 on the 21-item Hamilton Rating Scale for Depression (Hamilton, 1960) (mean score ± SD = 27.8 ± 3.1). The comparison group (n = 11) included two nonendogenous primary depressives, three patients suffering from minor depressive disorder, two manics, one patient suffering from panic disorder, and three schizophrenics (seven males and four females; age range: 27-63 years; mean: 39.9 ± 11.3 years). Individual diagnosis, sex, and age are displayed in Table 1. Two patients were bipolar I; none was psychotic. The predominance of male patients in this sample, as opposed to the general 2:1 female:male ratio among depressive inpatients, results from the gender repartition of beds in the Psychopharmacology Unit, mainly devoted to psychoneuroendocrinological research in which male patients are often preferred.

Patients were free of medical illness, as evidenced by history, physical examination, electrocardiogram, electroencephalogram, chest X-ray, and routine laboratory tests. They had also been free of any medication for at least 2 weeks at the time of the study.

DST Procedure. The DST was performed according to the simplified procedure standardized by Carroll et al. (1981). A basal sample was collected at 8 a.m. on day 1, and oral dexamethasone, 1 mg, was administered by a nurse at 11 p.m. A postdexamethasone sample was collected at 4 p.m. on day 2. Nonsuppression was defined as a cortisol level above 5 μg/dl.

Immediately after each blood sampling, patients were asked to collect about 1 ml of whole saliva in a small plastic container which was frozen at -20°C until analysis.

Cortisol Assays. Plasma total and saliva cortisol concentrations were determined by radioimmunoassay (RIA), using ^{125}I-cortisol (Farmos Diagnostica, Finland) and anticortisol antiserum (made against the 3-CMO-BSA conjugate), as described previously (Sulon et al., 1978). Total plasma cortisol was measured by direct RIA from samples of 25 μl, 40-fold diluted, and heated at 60°C for 30 minutes; saliva cortisol was measured from nonextracted saliva (25 μl), as we have found a very high correlation between extracted (with ethylacetate) and nonextracted saliva (r = 0.99, n = 20, $p < 0.001$), reported previously (Walker et al., 1978; Poland and Rubin, 1982) and confirming the absence of corticosteroid binding protein in saliva.

Free cortisol was measured by the equilibrium dialysis method. One ml of diluted serum (1/10) was dialyzed for 24 hours at 37°C against 1 ml of 0.05 molar phosphate buffer (pH 7.4) containing tritiated cortisol. Before dialysis, another 1 ml of diluted serum was treated at 60°C for 20 minutes in order to denature transcortin (a thermolabile α_2-globulin), then dialyzed as described above to determine the albumin-bound cortisol fraction (Demey-Ponsart et al., 1977).

All assays were processed in duplicate. For both plasma and saliva cortisol assays, the maximum intra- and inter-assay coefficients of variation were 4.3% and 8.3%, respectively, based upon multiple pool replicates.

Data Analysis. The results of the study were used to calculate the sensitivity, specificity, and diagnostic confidence of the DST, according to the definitions of Vecchio (1966): "sensitivity" referring to the proportion of endogenous depressives exhibiting DST nonsuppression; "specificity," to the proportion of patients in the comparison group exhibiting normal suppression; and "diagnostic confidence," to the proportion of nonsuppressors who were endogenous depressives.

Paired t tests were used to analyze the cortisol level differences between day 1 and day 2, and group t tests to analyze the differences between endogenous depressives and controls. The relationships among plasma total, plasma free, and saliva cortisol collected on day 1 or on day 2 were assessed using the Pearson product-moment correlation coefficient (one-tailed test). Since the cortisol concentrations tended to be log-normally distributed, the data were also analyzed using a natural log (ln) transformation.

Results

Individual values of total, free, and saliva cortisol before (day 1) and after (day 2) DST are displayed in Table 1 and Fig. 1. In the entire sample, on day 1, mean levels were 21.8 (4.9) μg/dl for plasma cortisol, 1.48 (0.84) μg/dl for free cortisol, and 465 (184) ng/dl for saliva cortisol. After dexamethasone (day 2), all cortisol levels were significantly decreased: 5.4 (3.6) μg/dl for total cortisol ($p < 0.001$), 0.15 (0.12) μg/dl for free cortisol ($p < 0.001$), and 74 (41) ng/dl for saliva cortisol ($p < 0.001$).

A comparison of endogenous depressives and other psychiatric patients is displayed in Table 2. On day 1, there was only a trend ($0.05 < p < 0.1$) toward higher mean free cortisol level in endogenous depressives, but by day 2, endogenous depressives exhibited significantly higher mean levels of plasma total cortisol ($p < 0.01$) and plasma free cortisol ($p < 0.05$), and a trend toward higher levels of saliva cortisol ($0.05 < p < 0.1$) that was significant using the ln transformed data ($p < 0.05$). Pearson correlation coefficients between the three different cortisol values on each day are displayed in Table 3. On day 1, there were clearly significant relationships between total and free plasma cortisol ($p < 0.001$) and between total or free plasma cortisol and saliva cortisol ($p < 0.001$). All these relationships became still more significant on day 2 ($p < 0.001$).

With regard to the standard cutoff criterion of total cortisol (5 μg/dl), 11 patients were nonsuppressors: 10 among the endogenous depressives and 1 among the comparison group. These results correspond to a sensitivity of 67%, a specificity of 91%, and a diagnostic confidence of 91%. Other cutoff limits do not improve the global results of the DST (Table 4).

With respect to plasma free cortisol, 0.15 μg/dl appeared to be the best cutoff limit, giving results equivalent to a cutoff limit of 5 μg/dl for total cortisol (sensitivity: 64%, specificity: 91%, and diagnostic confidence: 90%).

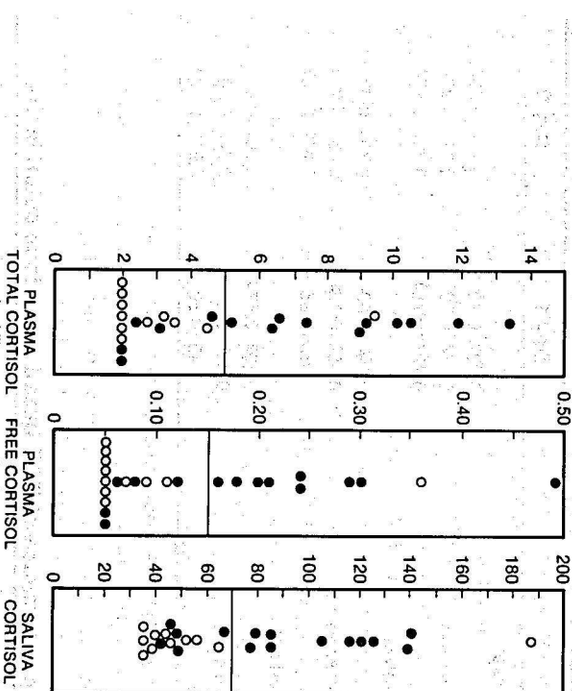
For saliva cortisol, the best cutoff limit appeared to be 70 ng/dl, giving the same sensitivity, specificity, and diagnostic confidence as 5 μg/dl of total cortisol (67%, 91%, and 91%).

Table 1. Sample and individual cortisol levels before (day 1) and after (day 2) DST

Patient No.	Sex	Age (years)	Diagnosis	Cortisol (day 1) Plasma total	Cortisol (day 1) Plasma free	Cortisol (day 1) Saliva	Cortisol (day 2) Plasma total	Cortisol (day 2) Plasma free	Cortisol (day 2) Saliva
1	M	61	Endogenous MDD, UP	22.8	1.09	497	10.1	0.29	85
2	M	29	Endogenous MDD, UP	26.7	1.43	430	9.0	0.18	77
3	M	42	Endogenous MDD, UP	16.8	0.62	137	11.9	0.30	120
4	M	47	Endogenous MDD, UP	21.6	1.17	428	10.5	—	140
5	M	40	Endogenous MDD, UP	21.8	1.65	771	3.1	0.08	42
6	M	54	Endogenous MDD, UP	15.4	0.86	286	6.6	0.24	85
7	M	18	Endogenous MDD, UP	23.2	2.27	455	2.4	0.06	46
8	M	31	Endogenous MDD, UP	21.0	1.81	605	< 2	< 0.05	67
9	M	50	Endogenous MDD, UP	21.0	1.6	509	5.2	0.16	79
10	M	50	Endogenous MDD, UP	25.0	1.63	624	4.6	0.12	48
11	F	66	Endogenous MDD, UP	29.3	2.06	650	7.4	0.20	116
12	F	29	Endogenous MDD, UP	30.4	3.92	697	6.4	0.21	125
13	F	51	Endogenous MDD, UP	27.5	3.82	702	< 2	< 0.05	49
14	M	55	Endogenous MDD, BP I	15.9	0.85	518	9.2	0.24	139
15	M	38	Endogenous MDD, BP I	21.4	1.19	225	13.4	0.49	105
16	M	32	Nonendogenous MDD, UP	20.8	1.33	576	< 2	< 0.05	40
17	F	30	Nonendogenous MDD, UP	23.9	1.33	640	< 2	< 0.05	56
18	M	30	Minor depression	19.3	0.47	447	< 2	< 0.05	< 35
19	M	41	Minor depression	16.6	0.84	193	2.7	0.07	46
20	F	39	Minor depression	17.3	0.91	211	< 2	< 0.05	< 35
21	F	51	Mania	12.9	0.63	502	< 2	< 0.05	< 35
22	F	46	Mania	31.5	1.67	581	4.5	0.11	39
23	M	51	Panic disorder	22.8	1.53	618	3.2	0.05	44
24	M	29	Schizophrenia	20.6	1.67	327	9.4	0.36	187
25	M	27	Schizophrenia	26.2	1.51	304	3.5	0.09	65
26	M	63	Schizophrenia	14.5	0.69	156	< 2	< 0.05	52

Plasma total and free values expressed as μg/dl; saliva values expressed as ng/dl. MDD = major depressive disorder; UP = unipolar; BP = bipolar.

Fig. 1. Distribution of individual cortisol levels at 4 p.m. after DST



Best cutoff limits are represented by a horizontal line.

Table 2. Cortisol levels before (day 1) and after (day 2) DST (mean ± SD)

	Endogenous depressives (n = 15) Mean	SD	Comparison group (n = 11) Mean	SD	p
Day 1					
Plasma total cortisol (μg/dl)	22.7	4.6	20.6	5.4	NS
(ln μg/dl)	3.10	0.21	2.99	0.26	NS
Plasma free cortisol (μg/dl)	1.73	0.98	1.14	0.44	$0.05 < p < 0.1$
(ln μg/dl)	0.42	0.52	0.05	0.44	$0.05 < p < 0.1$
Saliva cortisol (ng/dl)	502	183	414	182	NS
(ln ng/dl)	6.13	0.47	5.92	0.51	NS
Day 2					
Plasma total cortisol (μg/dl)	6.9	3.7	3.2	2.2	< 0.01
(ln μg/dl)	1.76	0.65	1.03	0.49	< 0.01
Plasma free cortisol (μg/dl)	0.19	0.12	0.09	0.09	< 0.05
(ln μg/dl)	-1.75	0.84	-2.66	0.61	< 0.01
Saliva cortisol (ng/dl)	87	35	57	44	$0.05 < p < 0.1$
(ln ng/dl)	4.38	0.43	3.91	0.48	< 0.05

Table 3. Pearson correlation coefficients between cortisol levels before (day 1) and after (day 2) DST[1]

	Day 1	Day 2
Total cortisol vs. free cortisol		
For: Whole sample	0.72[2] (0.79[2])	0.95[2] (0.95[2])
Endogenous depressives	0.77[2] (0.82[2])	0.94[2] (0.92[2])
Comparison group	0.79[2] (0.75[3])	0.98[2] (0.96[2])
Free cortisol vs. saliva cortisol		
For: Whole sample	0.59[2] (0.59[2])	0.79[2] (0.84[2])
Endogenous depressives	0.65[3] (0.72[2])	0.66[3] (0.79[2])
Comparison group	0.39 (0.35)	0.95[2] (0.83[2])
Total cortisol vs. saliva cortisol		
For: Whole sample	0.59[2] (0.57[2])	0.79[2] (0.82[2])
Endogenous depressives	0.60[3] (0.59[3])	0.74[2] (0.78[2])
Comparison group	0.49 (0.50)	0.91[2] (0.76[3])

1. In transformed data shown in parentheses.
2. $p < 0.001$.
3. $p < 0.01$.

Table 4. Diagnostic performance of DST based on various cutoff limits

Plasma total cortisol cutoff limit (μg/dl)	**3**	**4**	**5**	**6**	**7**
Sensitivity (%)	80	73	67	60	47
Specificity (%)	73	82	91	91	91
Diagnostic confidence (%)	75	85	91	90	87
Plasma free cortisol cutoff limit (μg/dl)	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**
Sensitivity (%)	71	64	50	21	13
Specificity (%)	82	91	91	91	91
Diagnostic confidence (%)	83	90	87	75	67
Saliva cortisol cutoff limit (μg/dl)	**50**	**60**	**70**	**80**	**90**
Sensitivity (%)	73	73	67	53	40
Specificity (%)	64	82	91	91	91
Diagnostic confidence (%)	73	85	91	89	86

Discussion

The results of this study support the findings of Carroll et al. (1981) of high sensitivity and specificity of the DST for diagnostic confirmation of endogenous depression. The findings on sensitivity are even slightly higher than in the studies of Carroll et al. (1981) using the same methodology (dexamethasone, 1 mg, and a single 4 p.m. blood sample) among inpatients (67% vs. 59%). Moreover, the RIA method used in this study to measure cortisol is generally more specific than the competitive-protein-binding method which Carroll et al. (1981) used to establish the 5 μg/dl cortisol cutoff, with the consequence that a lower cutoff (4 μg/dl) has been recommended (Carroll, 1982*a*). This lower cutoff would improve sensitivity in this study (to 73%), but with a decrease of the associated specificity (from 91% to 82%) and diagnostic confidence (from 91% to 85%). Most studies, however, have found generally lower diagnostic sensitivities (40-50%) (review in Carroll, 1982*b*). These discrepancies can result from many variables, related to patient, investigator, DST procedure, or exclusion criteria (review in Checkley and Rush, 1983). The good diagnostic performance of the DST in this study may be explained by the attentive screening (by two independent psychiatrists) of a small sample of definitely endogenously depressed patients characterized by a high severity level (a mean score of 27.8 on the Hamilton Rating Scale for Depression at the end of a 2-week washout period). In addition to the use of the 1 mg dexamethasone dose (more sensitive than the 2 mg dose), this longer than usual washout duration may contribute to the higher rate of nonsuppression.

The concentration of most biologically active compounds in saliva reflects the nonprotein-bound concentration of the compound in plasma (Horning et al., 1977). This is of clinical significance since it is now generally accepted that the biological activity of a steroid parallels the "free" hormone concentration. Saliva contains no corticosteroid-binding protein (Katz and Shannon, 1964) and appears to be ideal for the direct clinical determination of free cortisol without the need for tedious extraction.

Saliva cortisol presents a circadian rhythm very similar to plasma cortisol (Walker et al., 1978; Stahl and Dörner, 1982), responds to either painful or anxiety-provoking stimuli (Stahl and Dörner, 1982), and is sensitive to stimulation by ACTH or suppression by dexamethasone (Shannon et al., 1959*a*, 1959*b*, 1964, 1965, 1966*a*, 1966*b*; Katz and Shannon, 1964, 1969; Walker et al., 1978). The increase of saliva cortisol in Cushing's syndrome and after ACTH is even higher than indicated by total plasma cortisol and corresponds well to the plasma increase of free cortisol (Walker et al., 1978; Stahl and Dörner, 1982). Similarly, the very modest increase of unbound cortisol in plasma during the third trimester of pregnancy is accurately reflected in saliva, whereas total cortisol increases considerably due to an increased transcortin synthesis (Stahl and Dörner, 1982). In normal women taking estrogen-containing oral contraceptives, plasma cortisol levels are above normal values and the response to ACTH considerably exceeds normal. In contrast, both basal saliva cortisol values and response after ACTH are within the normal range (Stahl and Dörner, 1982). Comparison of cortisol concentrations in plasma, parotid saliva, and whole saliva after stimulation with ACTH and suppression with dexamethasone indicates that changes in plasma cortisol are accurately and immediately reflected in either the parotid or whole saliva (Walker et al., 1978). Moreover, saliva cortisol levels are independent of flow rate (Katz and Shannon, 1969; Walker et al., 1978). Taken together, these data suggest that saliva cortisol, like plasma free cortisol, is a more reliable index of adrenal function than plasma total cortisol.

We previously suggested that plasma free cortisol levels could successfully be used as an indicator of nonsuppression after DST in depression, with a sensitivity

somewhat higher than with total cortisol and with the same specificity (Ansseau et al., in press). Preliminary data from Poland and Rubin (1982) suggest that saliva cortisol levels could also be used in the DST: Six DST nonsuppressors (four of whom were endogenous depressives) exhibited higher saliva cortisol levels ($\geqslant$ 47 ng/dl) than 14 DST suppressors ($\leqslant$ 35 ng/dl). Our results support this finding: Saliva cortisol levels give the same level of diagnostic confidence as total or free plasma cortisol levels.

Collection of saliva is totally stress-free and prevents a possible artifact attendant to the stressful and possibly painful venipuncture procedure, especially in psychiatric patients who may have an acute response to anxiogenic stimuli. This factor could possibly increase DST diagnostic confidence. Our study does not permit an answer to this question, since saliva collection was always performed *after* blood collection, in order to study correlations between cortisol levels, and thus is supposed to reflect the same level of stress-response, although the time course of cortisol increase in plasma and saliva cortisol following venipuncture may be slightly different. This issue deserves to be tested in a followup study in which saliva cortisol is obtained both before and after venipuncture. Moreover, the DST with saliva cortisol measurement can be performed more easily, especially in outpatients who could perform the DST at home, without need for a nurse for blood collection, simply by taking dexamethasone, 1 mg, at 11 p.m., collecting 1 ml of saliva at 4 and 11 p.m. on the following day, and freezing samples at home until carrying them to the laboratory. Saliva DST could also be used in those situations where measurement of plasma total cortisol results in an invalid DST, e.g., during pregnancy or in patients taking oral contraceptives.

Thus, saliva cortisol measurement may offer a real improvement in both accuracy and ease of DST procedure; however, the best cutoff limit needs to be verified in a larger sample of patients.

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