0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 85, No. 10
Printed in U.S.A.

The Desmopressin Test in the Differential Diagnosis between Cushing's Disease and Pseudo-Cushing States

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ABSTRACT

Differentiating Cushing's disease (CD) from pseudo-Cushing (PC) states may still be difficult in current practice. Because desmopressin (1-deamino-8D-arginine vasopressin, DDAVP), a vasopressin analogue, stimulates ACTH release in patients with CD but not in the majority of normal, obese, and depressed subjects, we investigated its ability to discriminate CD from PC states. One hundred seventy-three subjects (76 with active CD, 30 with PC, 36 with simple obesity, and 31 healthy volunteers) were tested with an iv bolus of 10 μg DDAVP. Sixty-one of these subjects also underwent a control study with saline. DDAVP induced marked ACTH and cortisol rises in CD ($P < 0.005$ *vs.* saline, for both ACTH and cortisol) but not in PC. A significant ACTH elevation occurred upon DDAVP administration also in normal and obese subjects, but it was much smaller than that observed in patients with CD ($P < 0.0001$). A peak absolute ACTH increase ($\geq$6 pmol/L), after DDAVP, allowed us to recognize 66 of 76 patients with CD and 88 of 97 subjects of the other groups. The same criterion correctly identified 18 of 20 patients with mild CD (24-h urinary free cortisol $\leq$ 690 nmol/day) and 29 of 30 PC, resulting in a diagnostic accuracy of 94%, which was definitely higher than that displayed by urinary free cortisol, overnight 1-mg dexamethasone suppression test, and midnight plasma cortisol. In conclusion, the DDAVP test seems to be a useful adjunctive tool for the evaluation of hypercortisolemic patients chiefly because of its ability to differentiate mild CD from PC states. (*J Clin Endocrinol Metab* **85:** 3569–3574, 2000)

SEVERAL TESTS have been proposed to differentiate mild forms of Cushing's disease (CD) from pseudo-Cushing (PC) states. These latter classically include patients with major depression, alcoholism and alcohol-withdrawal syndrome, severe truncular obesity, and poorly controlled non-insulin-dependent diabetes mellitus. Furthermore, some patients with polycystic ovary syndrome exhibit clinical and biochemical features of Cushing's syndrome (CS) (1–3). The commonly used screening tests for CS, *e.g.* the 24-h urinary free cortisol (UFC) determination, the 1-mg overnight suppression test (OST), and the standard low-dose (48-h, 2 mg/day) dexamethasone suppression test (4, 5), have been largely validated but their specificity is suboptimal. A single midnight serum cortisol measurement, the patient being asleep (6) or awake (7, 8), seems able to distinguish patients with CS from normal subjects (6) and patients with PC (7, 8). However, this test necessitates hospitalization, and this argues against its use in a routine outpatient setting. The CRH test with dexamethasone pretreatment (9), the late night (10, 11) and dexamethasone-suppressed salivary cortisol determination (12), and the overnight UFC measurement (13) have also been described as useful tools for the evaluation of hypercortisolemic patients but, to date, await a more systematic evaluation.

Testing with desmopressin (1-deamino-8D-arginine vasopressin, DDAVP), a long-acting vasopressin analogue acting mainly on the V2 receptor and with a weak reactivity for the V1b (V3) receptor (14, 15), has been proposed as a useful procedure for the differential diagnosis of CS, because it seems able to elicit an ACTH and cortisol release in patients with CD but not in the majority of normal, obese, and depressed subjects and patients with ectopic ACTH syndrome (16–24). However, the published criteria for the DDAVP test are still largely arbitrary and generally established on small series of subjects. In particular, no studies have investigated the ability of the DDAVP test to differentiate CD from PC states. In order to evaluate this aspect, we have studied the pattern of plasma ACTH and cortisol secretion after administration of DDAVP in patients with CD, PC, and uncomplicated simple obesity and in normal volunteers. In subgroups of the same subjects, a control study with administration of saline was also performed.

Received November 18, 1999. Revision received April 19, 2000. Accepted June 29, 2000.

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Subjects and Methods

Subjects

A total of 173 subjects were studied: 76 with active CD, 30 with PC, 36 with uncomplicated simple obesity, and 31 normal-weight healthy volunteers. All subjects had not been taking medications for at least 6 weeks before the study. The diagnosis of CS was based on 3 (24-h) UFC measurements, cortisol circadian rhythm, and suppressibility with OST in all cases and, additionally, on the standard low-dose dexamethasone suppression test in 22 patients. Preoperative diagnosis of CD was suggested by ACTH and cortisol responsiveness to CRH testing, cortisol suppression after high-dose dexamethasone suppression test, and (when performed) evidence of pituitary source of ACTH secretion on bilateral inferior petrosal sinus sampling. A pituitary adenoma was disclosed in 46 patients (macroadenoma in 8 cases) at magnetic resonance and/or computed tomography. The diagnosis of CD was confirmed in 67 cases at pituitary surgery and by postoperative clinical and

biochemical resolution of the hypercortisolism in the remaining 9. Patients with PC had cushingoid features, *e.g.* visceral obesity, purple striae, hyperthrichosis, and hypertension, with mildly increased UFC levels (range, 223.5–681.5 nmol/day) associated with inconstantly elevated midnight and dexamethasone-suppressed plasma cortisol values. In particular, 2 subjects had alcoholic PC, and 7 suffered from major depression diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (25). In addition, 10 patients with PC were diagnosed to have polycystic ovary syndrome, based on clinical, hormonal, and ecographic criteria (2). In all patients with PC, a 2-yr follow-up did not show any progression towards overt CD. Obese subjects and normal volunteers were disease-free, none had evidence of any psychiatric disorder, and all had hormonal evaluation negative for CS (normal UFC and plasma cortisol values). The waist circumference was measured midway between the lowest rib and iliac crest, the hip circumference estimated at the level of great trochanters, and their ratio (waist-to-hip ratio) calculated. Clinical and biochemical details of the subjects are shown in Table 1.

Study design

The study was approved by the Ethical Committee of our Institution and informed consent obtained from all participants. After an overnight fast, all subjects underwent a 10 μg DDAVP (Minirin/DDAVP, Ferring Pharmaceuticals Ltd., Malmo, Sweden) administration as slow iv bolus. In 61 subjects (17 CD, 14 PC, 18 obese and 12 normal volunteers) a control study with saline administration was also performed. Serial blood samples for ACTH and cortisol estimation were obtained from an indwelling catheter inserted in a forearm vein 30 min before, basally and 15, 30, 45, 60, 90, and 120 min after drug or saline. Blood pressure and heart rate were monitored throughout the experiment. Subjects were advised to restrict fluid intake to 2 L during the study day.

Assays

Blood samples were collected into prechilled glass tubes containing EDTA-Trasylol, centrifuged at 4 C, and the plasma stored at −20 C until assayed. Plasma ACTH was measured by two-site immunoradiometric assay (Allegro, Nichols Institute Diagnostics, San Juan Capistrano, CA). Plasma cortisol and UFC, the latter after urine extraction with dichloromethane, were measured by RIA, (Byk-Sangtec Diagnostica, Dietzenbach, Germany and DPC, Los Angeles, CA, respectively). Sensitivity of the methods is 0.5 pmol/L for ACTH and 13.8 nmol/L for plasma cortisol and UFC. Intra- and interassay coefficients of variations are 3.2 and 8.2% for ACTH, 3.0 and 4.7% for plasma cortisol, and 3.5 and 6.2% for UFC. Normal ranges in our laboratory are 2.2–11.0 pmol/L for ACTH, 138–690 nmol/L for 0900-h plasma cortisol, and 27.6–220.7 nmol/day for UFC.

Statistical analyses

Data were analyzed using StatView 4.5 software (Abacus Concepts, Berkeley, CA). Hormonal secretory responses are expressed as absolute peak values, absolute increments over baseline values, and areas under the curve (AUCs) determined by the trapezoidal method. Both total and incremental AUCs were calculated and used for intragroup and intergroup comparisons, respectively. Results are presented as mean ± SEM. Intragroup statistical evaluation was carried out by paired Student's *t* test, whereas intergroup differences were evaluated by ANOVA followed by Fisher *post-hoc* test. Correlations between basal plasma cortisol and ACTH and cortisol responses to DDAVP were established by linear regression analysis. Sensitivity, specificity, diagnostic accuracy, and predictive values were calculated according to standard statistical methods (26). Receiver-operator-characteristic (ROC) curves were used to establish the usefulness of each parameter of the DDAVP test for the differentiation of CD from the other groups (27).

Results

Compared with saline, injection of DDAVP evoked a clear-cut increase of both ACTH and cortisol plasma levels in patients with CD ($P < 0.005$) but not in patients with PC. A modest, though statistically significant, rise of ACTH levels was observed also in obese and normal subjects ($P < 0.005$ and $P < 0.05$, respectively).

On DDAVP administration, only slight (not significant) plasma cortisol elevations occurred in patients with PC, in obese patients, and in normal volunteers. In these subjects, the ACTH and cortisol rises were definitely lower than the ones displayed by patients with CD ($P < 0.0001$). There were no significant differences in the hormonal responses to DDAVP among patients with PC, obese patients, and healthy subjects. Results are shown in Table 2.

As concerns the diagnostic power of the test, if the criterion proposed by Malerbi and co-workers (cortisol increase over baseline of 12%, *i.e.* 4-fold the intraassay coefficient of variation) (17) is applied to our data, most study subjects seem to be responsive to DDAVP. Likewise, adopting the criteria used for the CRH test (ACTH and cortisol rise over baseline ≥35% at 15–30 min and ≥20% at 30–45 min, respectively) (21, 28), as many as 71 subjects are misclassified with a consequent unacceptably low diagnostic accuracy. Conversely, a criterion based on an absolute ACTH increase over baseline equal or greater than 6 pmol/L, as indicated by ROC analysis, correctly identified 66 of 76 patients with CD and 88 of 97 subjects of the other groups (Fig. 1), resulting in a sensitivity of 86.8% and a specificity of 90.7% (Table 3). The ROC curves for the absolute and percent increments of ACTH and cortisol after DDAVP are shown in Fig. 2. Conversely, when only CD patients with mildly elevated UFC levels (≤690 nmol/day; n = 20) were compared with PC patients (n = 30), the same criterion yielded a sensitivity of 90%, a specificity of 96.7%, and a diagnostic accuracy of 94% that was definitely higher than that displayed by UFC, OST, and midnight plasma cortisol (Table 4).

Pooling the data of normal and obese subjects and patients

TABLE 1. Characteristics of the study subjects

Subjects	Gender (M/F)	Age, yr (range)	BMI (kg/m^2)	WHR	0900-h ACTH (pmol/L)	Midnight cortisol (nmol/L)	OST[a] cortisol (nmol/L)	UFC (nmol/day)
Cushing's disease	13/63	34.6 (11–75)	30.2 ± 2.01	0.92 ± 0.05[b]	17.7 ± 2.26	474.5 ± 44.42	430.4 ± 72.84	818.0 ± 122.14
Pseudo-Cushing	10/20	30.0 (14–55)	35.2 ± 1.97[b]	0.93 ± 0.05[b]	5.0 ± 0.52[c]	182.1 ± 43.59[c,d]	93.8 ± 48.28[c,d]	321.7 ± 27.81[c,d]
Obese	6/30	34.9 (16–65)	38.5 ± 1.03[b]	0.95 ± 0.03[b]	4.3 ± 0.37[c]	118.6 ± 22.07[c]	24.8 ± 2.76[c]	137.4 ± 10.57[c]
Normal subjects	8/23	28.7 (18–60)	23.5 ± 0.73	0.82 ± 0.02	4.0 ± 0.40[c]	46.9 ± 4.69[c]	19.3 ± 1.38[c]	113.9 ± 12.99[c]

Data are expressed as mean ± SEM. BMI, Body mass index; WHR, waist-to-hip ratio.
[a] 1-mg overnight dexamethasone suppression test.
[b] $P < 0.0001$ *vs.* normal subjects.
[c] $P < 0.0001$ *vs.* Cushing's disease.
[d] $P < 0.01$ *vs.* normal subjects.

TABLE 2. Plasma ACTH and cortisol levels in response to DDAVP administration

Subjects	ACTH				Cortisol			
	AUC_{saline} [a]	AUC_{ddavp} [a] (pmol/L·120 min)	ΔAUC_{ddavp} [b]	$Peak_{ddavp}$ [b] (pmol/L)	AUC_{saline} [a]	AUC_{ddavp} [a] (nmol/L·120 min)	ΔAUC_{ddavp} [b]	$Peak_{ddavp}$ [b] (nmol/L)
Cushing's disease	1558.6 ± 154.10	2717.7 ± 262.27[c]	1066.2 ± 273.90	37.1 ± 5.26	49835.8 ± 2435.37	79326.8 ± 6908.26[c]	19622.0 ± 6275.90	816.7 ± 76.15
Pseudo-Cushing	615.4 ± 35.81[d]	634.0 ± 56.87	28.9 ± 31.71[d]	7.6 ± 0.65[d]	42152.0 ± 4486.41	43012.8 ± 2596.77	0.3 ± 2388.74[d]	469.0 ± 24.00[d]
Obese	481.8 ± 43.74[d]	661.35 ± 61.78[c]	164.4 ± 32.52[d]	7.7 ± 0.74[d]	26025.6 ± 2479.24	30484.2 ± 2122.12	706.3 ± 1933.23[d]	333.8 ± 18.21[d]
Normal subjects	422.5 ± 51.44[d]	497.7 ± 54.55[e]	104.2 ± 31.96[d]	5.9 ± 0.71[d]	29885.5 ± 2872.95	33988.1 ± 2086.91	−3412.9 ± 2181.54[d]	372.5 ± 28.97[d]

[a] Total AUC (n = 61).
[b] Incremental AUC and absolute peak values (n = 173). Data are expressed as mean ± SEM.
[c] $P < 0.005$ *vs.* saline.
[d] $P < 0.0001$ *vs.* Cushing's disease.
[e] $P < 0.05$ *vs.* saline.

FIG. 1. Peak absolute ACTH increase over baseline, after DDAVP, in patients with CD, in patients with PC, and in obese and normal subjects.

with PC (n = 97), an inverse correlation was found between baseline cortisol values and the incremental AUC of ACTH ($r = -0.373$, $P = 0.0002$) (Fig. 3A) and cortisol ($r = -0.626$, $P < 0.0001$) after DDAVP stimulation (Fig. 3B). In contrast, no correlation was found in patients with CD.

Most subjects experienced mild and short-lived facial flushing immediately after DDAVP administration. No significant cardiovascular and gastrointestinal untoward reactions were observed during the study.

Discussion

The present study has shown that testing with DDAVP is a valuable aid in distinguishing patients with CD from patients with PC. Indeed, administration of DDAVP in CD elicited a rise in plasma ACTH and cortisol levels that was much higher than the one evoked in the other groups. However, when compared with saline, ACTH secretion was significantly stimulated by DDAVP injection also in normal and obese subjects. This is in contrast to most (16–23), but not all (29, 30), of the previous reports that failed to show appreciable ACTH responses to DDAVP in healthy volunteers. The lack of control studies with saline, the small number of subjects investigated, and the different criteria used to evaluate the responses may account for these discrepancies. On the other hand, V1b pituitary receptors have been identified also in the normal pituitary (31–33), and this may explain the

TABLE 3. Performance characteristics of tests used in all subjects for the diagnosis of Cushing's disease

Criterion	Sensitivity (%)	Specificity (%)	+Predictive value	−Predictive value	Diagnostic accuracy (%)
After DDAVP stimulation					
Peak cortisol increase > 4-fold CV[a]	86.8	38.1	0.52	0.78	59.5
Peak cortisol increase ≥ 220 nmol/L[b]	65.8	88.7	0.82	0.77	78.6
Cortisol increase ≥ 20% at 30–45 min[c]	72.4	48.5	0.52	0.69	59.0
Peak cortisol increase > 25%[b]	77.6	50.5	0.55	0.74	61.8
ACTH increase > 35% at 15–30 min[c]	84.2	43.3	0.54	0.78	61.3
Peak ACTH increase > 115%[b]	57.9	75.3	0.65	0.70	67.6
Peak ACTH increase ≥ 6 pmol/L[b]	86.8	90.7	0.88	0.90	89.0
UFC > 221 nmol/day[d]	92.1	66.0	0.69	0.90	77.5
OST (F > 138 nmol/L)	97.4	96.9	0.93	0.97	97.1
F 2400 h > 207 nmol/L	97.4	90.7	0.87	0.98	93.6

[a] Intraassay coefficient of variation at baseline (17).
[b] Cut-off values obtained from ROC analysis.
[c] (21, 28).
[d] Upper limit of reference range for UFC.

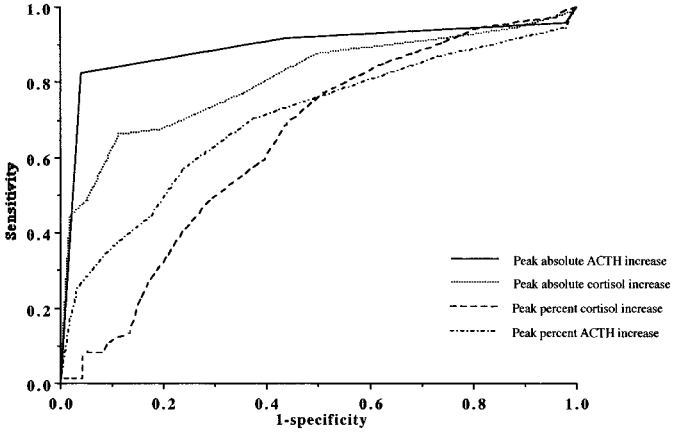

FIG. 2. ROC curves using absolute and percent increments of plasma ACTH and cortisol concentrations after DDAVP as criteria for the diagnosis of CD.

small, yet significant, ACTH response to DDAVP observed in our normal and obese subjects.

The reason for the exaggerated hormonal response to DDAVP in CD is still unknown. DDAVP has a high affinity for V2 receptors, but its effects on the ACTH-secreting cells are mediated by a specific V1b pituitary receptor (31, 32). Corticotroph tumors might, therefore, either overexpress the V1b receptor or express an ectopic V2 receptor (33). Glucocorticoids have been shown to up-regulate V1b receptors in the anterior pituitary of normal and vasopressin-deficient rats (34). However, the possibility that this mechanism underlies the enhanced corticotroph responsiveness to DDAVP in CD, as previously suggested (35), seems unlikely, in view of the absent ACTH response displayed by our patients with PC. On the contrary, an inverse correlation between baseline cortisol levels and the incremental AUCs of ACTH and cortisol after DDAVP was observed in these patients, as well as in normal and obese subjects. These findings are in accordance with the negative influence exerted by baseline plasma cortisol levels on the stimulated ACTH/cortisol secretion in physiological conditions and in patients with major depression (36) or anorexia nervosa (37), and this argues against a role of hypercortisolism in facilitating the response to DDAVP.

As regards the response criteria for the DDAVP test, both that proposed by Malerbi and co-workers (17) and that used for the CRH test (21, 28), failed to provide an acceptable diagnostic accuracy (Table 3). By contrast, in our population, a plasma peak ACTH increase equal to or greater than 6 pmol/L, as indicated by ROC analysis, allowed the best discrimination between patients with CD and the other groups, with a sensitivity of 86.8%, a specificity of 90.7%, and a diagnostic accuracy of 89% (Table 3). However, because the major diagnostic challenge resides in the differentiation of mild CD from PC states, we have compared the discriminative ability of DDAVP *vs.* the conventional screening tests in these two groups (Table 4). In this selected population, DDAVP showed a high specificity, because only 1 of 30 patients with PC exhibited an increment of plasma ACTH greater than 6 pmol/L after DDAVP administration (6.1 pmol/L) (Fig. 1). Interestingly, 29 of 30 patients with PC and increased UFC, and all patients with PC with unsuppressed cortisol after OST (n = 3) and elevated midnight plasma cortisol levels (n = 9), have been correctly identified as nonresponders to the DDAVP test. Thus, in spite of its suboptimal diagnostic accuracy displayed in the whole group, the DDAVP test enabled a good differentiation between mildly hypercortisolemic patients with CD and PC. These findings indicate that testing with DDAVP can be a useful second-line option in evaluating patients with moderate hypercortisolism.

A dexamethasone-suppressed CRH test has also been described as an accurate means to establish the diagnosis of CS in equivocal cases (9). In their series, Yanovski *et al.* reported that failure of plasma cortisol to suppress below 38.6 nmol/L 15 min after administration of CRH correctly identified all patients with CS. By this criterion, however, the test seems to be superfluous in those patients with CS already presenting plasma cortisol levels above this value after the standard low-dose dexamethasone suppression test, *i.e.* according to the literature, in at least 90% of cases (4, 6, 9, 38). In addition, the dexamethasone-suppressed CRH test is more burdensome and expensive, compared with the DDAVP test.

In conclusion, the DDAVP test seems to be a useful adjunct for the diagnosis of CD, chiefly because of its ability to

TABLE 4. Diagnostic power of different tests in the differentiation of mild Cushing's disease (UFC ≤ 690 nmol/day) (n = 20) from pseudo-Cushing states (n = 30)

Criterion	Sensitivity (%)	Specificity (%)	+Predictive value	−Predictive value	Diagnostic accuracy (%)
UFC > 221 nmol/day	70.0	0.0	0.32	0.0	28.0
OST (F > 138 nmol/L)	85.0	90.0	0.85	0.90	88.0
F 2400 h > 207 nmol/L	90.0	70.0	0.67	0.91	78.0
Peak ACTH increase ≥ 6 pmol/L[a]	90.0	96.7	0.95	0.94	94.0

[a] After DDAVP stimulation.

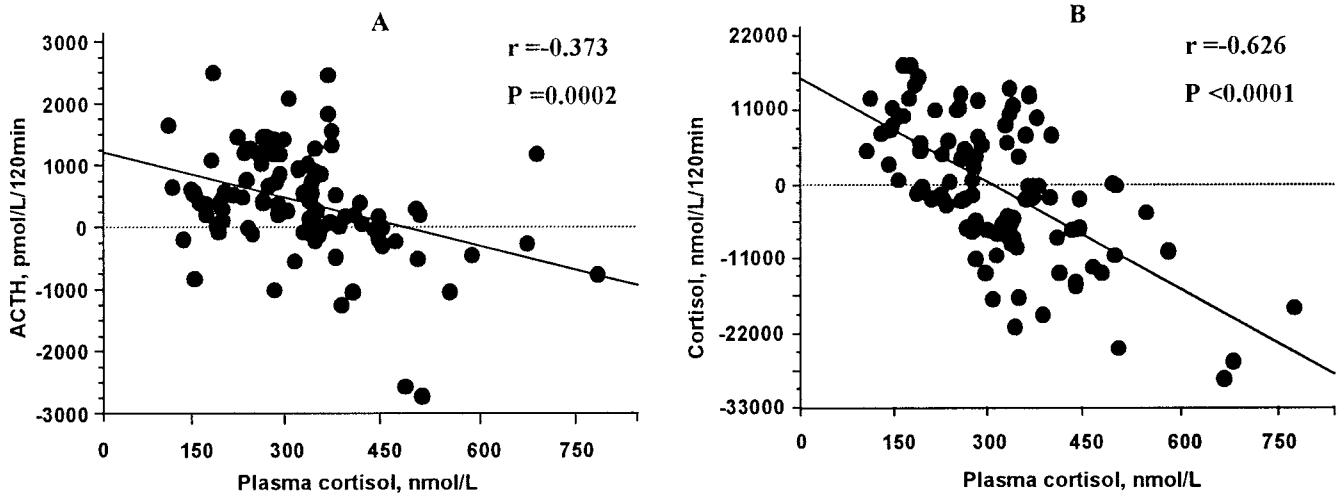

FIG. 3. Univariate linear regression analysis of incremental AUCs of ACTH (A) and cortisol (B) after DDAVP stimulation *vs.* baseline cortisol levels in patients with PC and in obese and normal subjects (n = 97).

recognize patients with PC states. Studies in patients with ectopic ACTH syndrome are now needed.

Acknowledgments

We are indebted to the nursing staff of the Endocrinology inpatient ward and the 6th floor outpatient clinic at the San Luca Hospital and to Dr. Simona Bonfanti for technical support and collaboration.

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