

"Normal Suppression" to Dexamethasone in Cushing's Disease: An Expression of Decreased Metabolic Clearance for Dexamethasone

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ABSTRACT. The adrenal cortical function of a patient with pituitary-dependent Cushing's syndrome exhibited normal responsiveness to conventional doses of dexamethasone (Dex) over several years of evaluation. "Periodic hormonogenesis" did not seem to explain the phenomenon. Plasma concentrations of Dex were measured to ascertain whether an abnormality in Dex me-

tabolism might explain the apparent discrepancy in Dex responsiveness. Plasma levels of Dex after oral administration of the steroid were higher than normal, suggesting that decreased clearance of Dex accounts for the phenomenon of "normal suppression" in this patient with Cushing's syndrome. (*J Clin Endocrinol Metab* 47: 667, 1978)

THE FAILURE of small doses of dexamethasone (Dex) to suppress the pituitary-adrenal axis, as described by Liddle (1), has come to be accepted as one of the more reliable aids in the diagnosis of Cushing's disease. However, a few cases have been reported in which this standard dose of Dex resulted in normal suppression (2-5).

We describe a case of Cushing's disease in which normal suppression of cortisol secretion occurred in response to even smaller than standard doses of Dex. By studying the metabolism of Dex, we have achieved a satisfactory explanation for this phenomenon.

Materials and Methods

Case history

A 49-yr-old black female was well until 8 yr before admission when she developed hypertension. Two years later, she noticed the onset of central obesity, facial rounding, and plethora. Over the next 6 yr, she developed increased facial hair, hy-

perpigmentation, easy bruising, muscle weakness, and periorbital edema. The diagnosis of insulin-dependent diabetes mellitus was made 10 months before admission. The patient was studied in three different institutions, but the diagnosis of Cushing's disease was rejected because standard low doses of Dex completely suppressed her glucocorticoid production.

Physically, she was a plethoric woman with trunkal obesity, "moon facies," and a "buffalo hump." There was marked hyperpigmentation of the skin of the extensor surfaces. The only suggestion of virilization was mild hirsutism. Her blood pressure was 200/100 and ophthalmological examination revealed marked arteriolar narrowing and arterio-venous nicking without hemorrhages or exudates. There were no visual field defects. The lungs were clear to auscultation; the heart was not enlarged, but there was a loud aortic second sound without gallop rhythm. The abdomen was soft without organomegaly. Routine laboratory studies were normal, with the exception of hyperglycemia (200-250/dl) and hypokalemia (2.5-3.0 milliequivalent (meq)/ml). x-Ray of the spine showed severe osteoporosis; x-ray of the chest was normal.

The patient was evaluated further for Cushing's disease as follows. Polytomograms of the sella turcica were normal. An adrenal venogram revealed enlargement of both adrenal glands; these measured approximately 5 × 9 cm in their vertical and

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horizontal diameters. The intraadrenal venous tributaries were uniformly stretched and spread apart without evidence of a focal mass lesion. These findings were consistent with bilateral adrenal hyperplasia.

Metabolic studies

During these studies, the patient was at bed rest and on a diet which limited sodium to 500 mg/day. Her medications included 750 mg α -methyl dopa and 40 mg furosemide daily. After collection of blood and urine samples for basal steroid measurements over a 3-day period, the following studies were performed: 1) Dex suppression test: 0.25, 0.5, and then 2 mg Dex were given every 6 h for consecutive 2-day periods. Plasma cortisol and ACTH were measured daily at 0800 and 2000 h. Urine was collected daily for the measurement of 17-hydroxysteroids (17-OHCS), 17-ketosteroids (17-KS), free cortisol, and creatinine. 2) Dex metabolism was studied in the patient and in 11 age- and sex-matched controls. Oral Dex (0.25, 0.5, and 1.0 mg) was given at midnight and blood samples were obtained at 0800 h for the measurement of cortisol and Dex. During the Dex suppression test, plasma samples for Dex concentration were obtained at 0800 h on the 2nd day that each dose was given. In addition, the free fraction of Dex was calculated on two determinations.

The patient underwent transsphenoidal hypophysectomy and hormone replacement with hydrocortisone (20 mg in the morning, and 10 mg in the evening, and 0.2 mg sodium L-T₄ was started. Histological study of her pituitary gland showed only mild eosinophilic cell hyperplasia without a microadenoma. Six months after surgery, serum electrolytes and fasting and 2-h postprandial blood sugars were normal. Her blood pressure was well controlled with 750 mg methyl dopa. The patient still had moderate central obesity, but her hyper-

pigmentation, periorbital edema, easy bruising ability, and severe weakness had disappeared. The plasma cortisol and 24-h urine 17-OHCS were normal with the doses of steroid replacement used.

Hormone assay methods

Plasma Dex was measured by the method of Meikle *et al.* (6) and the free fraction of Dex was determined in Dr. Meikle's laboratory by a method previously described (7).

Urinary 17-OHCS were measured by the method of Silber-Porter (normal values, 2.5-8.5 mg/day) (8), and the 17-KS were measured by the technique of Drechter *et al.* (normal values, 5-15 mg/day) (9). Urinary free cortisol was measured by the New England Nuclear modified RIA (normal, 20-90 μ g/day) (10). plasma cortisol was measured by the single antibody technique of Foster and Dunn (normal, 7-25 μ g/dl in the morning and 2-9 μ g/dl in the evening) (11). ACTH was measured by the method of Berson *et al.* (normal, 10-80 pg/ml) (12).

Results

Dex suppression test

The values for plasma cortisol, ACTH, and urinary 17-OHCS, 17-KS, and free cortisol before and during the 6-day administration of Dex are shown in Table 1.

Dex metabolism

Results of the plasma Dex and cortisol after oral Dex in the patient and the controls are shown in Table 2. The plasma Dex levels during the Dex suppression test on study days 5, 7, and 9 at 0800 h were 1133, 1533, (normal, 370 \pm 143 ng/dl; n = 11) and 5633 ng/dl (normal, 1316 \pm 475 ng/dl; n = 11), respec-

TABLE 1. Results of Dex suppression test

Day of study	Medication Dex (mg/24 h)	Plasma cortisol (μ g/dl)		Plasma ACTH (pg/ml)		Urinary 17-OHCS (mg/24 h)	Urinary 17-KS (mg/24 h)	Urinary free cortisol (μ g/24 h)
		a.m.	p.m.	a.m.	p.m.			
1	0	68	41	226		13	20	998
2	0	55	63	173	129	15	21	1078
3	0	38		71		15	17	717
4	1	62	35	87	12	18	23	950
5	1	4	4	0	0	8	10	81
6	2	5	5	0	0	2	12	26
7	2	6	5	0	0	2	4	8
8	8	3	2	0	0	1	4	6
9	8	3	2	0	0	1	2	2

TABLE 2. Plasma Dex and cortisol after oral Dex

Day of study	Oral Dex at midnight (mg)	Plasma Dex (ng/dl at 0800 h)	Plasma cortisol ($\mu\text{g}/\text{dl}$ at 0800 h)	Expected plasma Dex (ng/dl)	Expected plasma cortisol ($\mu\text{g}/\text{dl}$)
12	0.25	384	22.5	125 \pm 25	11.5 \pm 4.3
13	0.5	651	10.5	216 \pm 40	2.7 \pm 2.3
14	1.0	988	3.4	417 \pm 160	2.0 \pm 1.1

tively. The free fractions of Dex were 37.3% and 38.6% on two determinations. The normal mean nonprotein-bound fraction for Dex is $37.5 \pm 0.27\%$ (mean \pm SEM; $n = 64$) (7).

Discussion

A patient had clinical signs and symptoms of Cushing's disease for more than 6 yr. Although hypercortisolism was demonstrated, the diagnosis of Cushing's disease was excluded on three occasions because her adrenal cortex could be suppressed normally with the standard low dose of Dex. In this study, blood and urine samples collected for basal steroid determinations demonstrated marked hypercortisolism. Dex suppression testing was started at half of the low standard dose (0.25 mg Dex every 6 h for 2 days). On the 2nd day at this dosage (study day 5), the plasma and urinary free cortisol levels were normally suppressed. On the 1st day of the standard low dosage (study day 6), her adrenal cortex suppressed to a degree that satisfies every diagnostic criterion for "normal suppression" (13-16).

There are several possible explanations for the phenomenon of normal pituitary-adrenal responsiveness to Dex in patients with Cushing's disease. It is theoretically possible that a spontaneous decrease in the secretory activity of a pituitary tumor might coincide with administration of Dex, thus creating the mistaken impression of normal suppressibility. In fact, three cases of "periodic hormonogenesis" have been reported (17-19). However, this possibility was unlikely in our patient because she had the Dex suppression test performed five times during a 6-yr time period with reproducible responses. Changes in plasma binding of Dex also were excluded in our patient, who had a normal free fraction of Dex.

The phenomenon of "normal suppression"

by Dex in Cushing's disease might have been explained by the loss of feedback receptors for cortisol on ACTH or corticotropin-releasing factor (CRF)-producing cells with an intact receptor for Dex. It is also conceivable the patient had a CRF-producing tumor and that the effect of this hormone on pituitary stimulation of ACTH was sensitive to low doses of Dex. However, our patient clearly showed resistance to Dex suppression. Eight hours after 0.25 and 0.5 mg Dex (study days 12 and 13), the plasma concentrations of cortisol were 22.5 and 10.5 ng/dl, respectively, with plasma values of Dex of 384 and 651 ng/dl. The latter were more than double the normal expected values. Meikle *et al.* have demonstrated that plasma concentrations of Dex over 250 ng/dl invariably suppressed cortisol levels in normal unstressed individuals to less than 5 $\mu\text{g}/\text{dl}$ (10). It was only after a plasma level of Dex of 988 ng/dl (study day 14) that suppression was achieved in the present case.

In Cushing's disease, the response of the pituitary-adrenal axis to doses of exogenous steroids is qualitatively normal but quantitatively abnormal; this suggests retention of the normal physiological regulating mechanisms, but the set-point of control seems abnormally high. Normally, the mean level of Dex is 370 ± 143 ng/dl by the 2nd day of the "low dose Dex suppression test," and this results in marked suppression of ACTH in normal individuals. The mean level of Dex by the 2nd day of the high dose Dex suppression test is 1316 ± 475 ng/dl, which usually is high enough to suppress the adrenal cortex in Cushing's disease patients. In our patients, the plasma values of Dex on the 2nd day of half-dose and low dose Dex (study days 5 and 7) were 1133 and 1533 ng/dl, respectively.

These data suggest a reduced rate of clearance of Dex; consequently, a usual dose of

steroid resulted in an abnormally high level of the glucocorticoid which was sufficiently high to suppress ACTH. The explanation for her delayed metabolic clearance of Dex is not apparent. Dex is metabolized by the liver. The patient did not have liver disease, she was not taking drugs that are known to decrease the activity of hepatic drug-metabolizing enzymes, and she was not in heart failure. Severe congestive heart failure was believed to be the cause of abnormally high plasma levels of Dex in a single patient with Cushing's disease (5).

Several proven cases of Cushing's disease have been reported to suppress normally in response to Dex (2-4). Abnormally high plasma levels of Dex, as seen in the present patient, might offer an explanation for the phenomenon of "normal suppression" to Dex. In such cases, the simultaneous measurement of Dex and cortisol could provide the clinician with a reliable test to confirm the diagnosis of Cushing's disease.

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