Suppression of cortisol secretion by low-dose dexamethasone testing in Cushing's disease

Case report

LUCILLE W. KING, M.D., KALMON D. POST, M.D., ISRAEL YUST, M.D., AND SEYMOUR REICHLIN, M.D., PH.D.

Department of Endocrinology, Tufts-New England Medical Center, Boston, Massachusetts, The Neurological Institute, Columbia-Presbyterian Medical Center, New York, New York, and Department of Medicine, Ichioov Hospital, Tel Aviv, Israel

Pituitary-adrenal function in a patient with classical features of Cushing's disease, increased urinary excretion of cortisol, and documented pituitary adenoma was found to be suppressed by dexamethasone in doses even less than those required to inhibit secretion in normal individuals. This response was shown to be due to inappropriately high levels of dexamethasone in plasma, presumed to be the consequence of decreased peripheral clearance. Because the dexamethasone suppression test is so widely used for diagnosis of Cushing's disease, it is important to recognize that this situation can occasionally occur.

KEY WORDS • Cushing's disease • pituitary tumor • adenoma • dexamethasone • cortisol • adrenal gland

Dexamethasone suppression tests, first described by Liddle, are widely used for the diagnosis of Cushing's disease. The so-called "low-dose" dexamethasone test (2 mg/day) will usually not suppress the secretion of cortisol in patients with Cushing's disease (bilateral adrenal hyperplasia). However, "high-dose" dexamethasone (8 mg/day) will generally suppress secretion in patients with Cushing's disease, but not in patients with other causes of cortisol hypersecretion such as adrenal adenoma or carcinoma, and ectopic adrenocorticotropic hormone (ACTH) secretion. Because these tests have become so important in differential diagnosis, exceptions to the general rule have received much attention.

One such exception is the finding that administration of low doses of dexamethasone will occasionally suppress cortisol secretion in Cushing's disease. Meikle and his colleagues have shown that abnormal clearance of dexamethasone may account for this finding, and have developed criteria for the recognition of this unusual manifestation. We report here a patient with Cushing's disease, proven by adenomectomy, who showed suppression of cortisol secretion with the standard low-dose dexamethasone test, even with doses below those usually required to suppress secretion in normal individuals.

Case Report

This 44-year-old woman was well until approximately 5 years prior to admission, when she developed occasional palpitations unrelated to exertion and not associated with chest pain. Two years before admission, she noted severe wheezing. At that point, she was found to be markedly hypertensive, and to have chronic obstructive pulmonary disease. She was given antihypertensive medications and a bronchodilator. Over the ensuing 2 years, muscle weakness, central obesity, amenorrhea, hyperpigmentation, easy bruisingability, and hypertrichosis developed.

Evaluation at Ichioov Hospital 1 year before admission revealed the following: morning (a.m.) blood cortisol levels were 22, 33, and 20 μg/dl, with corresponding evening (p.m.) cortisol levels of 18.5, 17.5, and 23 μg/dl; urinary free cortisol was 135 μg/total volume (normal 20 to 90 μg/total volume), which fell to 33 and 0 μg/total volume during dexamethasone testing with 2 and 8 mg/day, respectively. X-ray films of the skull and sella turcica, and computerized to-
TABLE 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3*</th>
<th>Day 4</th>
<th>Day 5†</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8§</th>
<th>Day 9</th>
<th>Day 10</th>
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</thead>
<tbody>
<tr>
<td>plasma cortisol (µg/dl)</td>
<td></td>
<td></td>
<td>20.0</td>
<td>3.7</td>
<td>3.2</td>
<td>3.6</td>
<td>4.0</td>
<td>19.0</td>
<td>11.4</td>
<td>4.3</td>
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<td>24-hr urinary free cortisol</td>
<td>235</td>
<td>419</td>
<td>127</td>
<td>85.5</td>
<td>81.5</td>
<td>39.4</td>
<td>122.0</td>
<td>88.8</td>
<td></td>
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<tr>
<td>(µg/total vol)</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>free cortisol/mg creatinine</td>
<td>.248</td>
<td>.436</td>
<td>.128</td>
<td>.074</td>
<td>.088</td>
<td></td>
<td></td>
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<tr>
<td>urine volume (cc)</td>
<td>875</td>
<td>1300</td>
<td>1580</td>
<td>3040</td>
<td>1850</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>creatinine (mg/dl)</td>
<td>108</td>
<td>72</td>
<td>63</td>
<td>38</td>
<td>50</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>plasma dexamethasone level (ng/dl)</td>
<td>919</td>
<td>596</td>
<td>2607</td>
<td>3245</td>
<td>694</td>
<td>423</td>
<td></td>
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</tbody>
</table>

* Administration of 0.5 mg dexamethasone every 6 hours for eight doses begun.
† Administration of 2 mg dexamethasone every 6 hours for eight doses begun.
§ Administration of 0.25 mg dexamethasone every 6 hours for eight doses begun.

mography (CT) of the adrenal glands, were reportedly normal on two occasions. She was admitted to the Clinical Study Unit at the New England Medical Center for further investigation.

Examination. On admission, the patient exhibited most of the classic findings of hypercortisolemia. She was plethoric, and had truncal obesity, rounded facies, and a prominent dorsal fat pad. She had numerous ecchymoses, especially on her arms, and had facial hirsutism. Proximal muscle wasting and weakness of the extremities were striking, and blood pressure was 142/98 mm Hg. A tinea versicolor infection was present over the thorax. Funduscopic examination was unremarkable. The thyroid was not palpable. Occasional expiratory wheezes were noted on auscultation of the lung fields. An $S4$ gallop was present. The abdomen was soft and without striae, organomegaly, or masses. The neurological examination was otherwise normal.

Plasma electrolytes, complete blood count, fasting blood glucose, routine liver function tests, and thyroid hormone levels were normal. The electrocardiogram was within normal limits, and the chest x-ray film demonstrated minimal cardiomegaly. Pulmonary function tests revealed mild chronic obstructive lung disease. The a.m. plasma level of cortisol was 22.6 µg/dl and that of ACTH was 77 pg/ml (Nichols Institute: normal 20 to 90 pg/ml).

Pluridirectional tomography of the sella turcica was interpreted to show erosion of the anteroinferior aspect of the sella floor, consistent with an intrasellar tumor. A CT scan of the skull was within normal limits.

Because Cushing's disease was strongly suspected on clinical grounds, dexamethasone suppression testing was repeated with low-dose, high-dose, and half the standard low-dose (1 mg per day) administration. Plasma cortisol and dexamethasone levels were obtained; the latter were measured by radioimmunoassay by Dr. Meikle, University of Utah, School of Medicine, Salt Lake City (Table 1). Because the clinical presentation was so striking, and in light of laboratory investigations, it was thought that the patient was indeed suffering from Cushing's disease, despite normal dexamethasone suppression.

Operation. Transsphenoidal exploration of the sella turcica was carried out. At surgery, the sella was noted to be slightly thinned on the left side inferiorly. On the surface of the pituitary gland a reddish tumor, 6 mm in diameter, was seen, which extended to a depth of only 1 mm (Fig. 1). A partial empty sella defect was also present. Exploration of the remainder of the gland did not disclose any other abnormalities. The pituitary tumor was removed, and biopsies of the surrounding gland taken.

Postoperative Course. The patient had a transient attack of diabetes insipidus, which resolved. Plasma cortisol levels were below normal, equaling 1.7 µg/dl at 44 hours after the last dose of 0.25 mg of dexamethasone. Free cortisol values in the urine were also low, ranging from 8 to 10 µg/day. Therefore, the patient was begun on cortisone replacement with 37.5 µg/day.
mg cortisone acetate daily. The thyroxine level remained unchanged. Within a few days after surgery, the patient's facial pigmentation lightened, she began to lose weight, and muscle strength improved. Over the ensuing weeks, her menses resumed and her energy level increased, as did a sense of well-being. Blood pressure fell to 130/90 mm Hg without the use of antihypertensive medications. Follow-up study 10 months after adenomectomy showed the patient to be normotensive and clinically well. Steroid replacement was gradually tapered off over 9 months. During an ACTH stimulation test, the cortisol level rose to a peak value of 34 μg/dl. However, urinary free cortisol was 4.7 μg at 10 months after adenomectomy, and the patient demonstrated a subnormal cortisol response to insulin-induced hypoglycemia. Because of these findings, steroid replacement with 12.5 mg of cortisone acetate was reinstituted. She again underwent dexamethasone suppression testing using 0.125 mg/6 hours for eight doses (Table 2).

Pathological Examination. Serial sections of the surgical specimen revealed a rim of adenoma, four to 10 cells thick at the edge of the specimen, which had occasional clusters of hyperchromatic nuclei and contained faintly staining periodic acid-Schiff-positive granules (Fig. 2).

Discussion

In this patient, the clinical features and consistently elevated 24-hour urinary free cortisol levels argued strongly for the presence of Cushing's disease; but plasma cortisol levels were unexpectedly suppressed to normal values during standard dexamethasone testing.

Meikle, et al., have studied the relationship between plasma dexamethasone and cortisol levels in normal subjects and patients with Cushing's syndrome during suppression tests. They found that dosage schedules of 0.5 mg and 2 mg every 6 hours for eight doses produced dexamethasone levels at 8 a.m. (6 hours after the last dose) of 370 ± 143 ng/dl and 1316 ± 475 ng/dl, respectively. In a series of patients with Cushing's syndrome, the same dosage schedules produced similar dexamethasone levels of 366 ± 134 ng/dl and 1440 ± 593 ng/dl. Plasma cortisol levels in normal subjects were suppressed to less than 5 μg/dl when plasma dexamethasone levels were above 200 ng/dl. In their series, plasma cortisol levels were not suppressed in four patients with adrenal tumors, whereas there was a variable but definite cortisol suppression in six patients with bilateral adrenal hyperplasia when dexamethasone levels were greater than 800 ng/dl.

Two patients with Cushing's disease in whom low-dose dexamethasone administration led to cortisol suppression were also studied by Meikle and associates. They found that the usual dose of dexamethasone led to abnormally high drug levels, which were sufficient to suppress ACTH secretion. When one of these patients was given smaller doses (0.25 mg and 0.50 mg) of dexamethasone, cortisol values 8 hours later were not suppressed, despite dexamethasone levels of 384 and 651 ng/dl, indicating the presence of resistance to dexamethasone suppression consistent with the diagnosis of Cushing's disease.
In the patient reported here, plasma cortisol secretion was suppressed by standard dexamethasone testing. To investigate these findings further, we obtained simultaneous plasma levels of dexamethasone and cortisol during standard suppression testing and also observed the response to a lower dose of dexamethasone (0.25 mg every 6 hours). On several occasions, dexamethasone levels were higher than predicted. For example, on Day 2 at the completion of high-dose administration, the dexamethasone level in our patient was 3245 ng/dl, which was approximately 2.89 times higher than expected. A dexamethasone level of 694 ng/dl, which is normally sufficient to suppress cortisol levels to less than 5 μg/dl, was associated with a plasma cortisol value of 11.4 μg/dl, thus indicating lack of suppressibility compatible with the diagnosis of Cushing’s disease. It is noteworthy that this was observed during the course of administration of dexamethasone at only 1 mg/day, which produced suppression of plasma cortisol to 4.3 μg/dl by the 2nd day. To our knowledge, this phenomenon has not been reported in the literature so far. After the adrenalectomy, our patient demonstrated suppression of plasma cortisol levels in response to dexamethasone (0.5 mg/day). While plasma levels of the drug were again higher than predicted for the dosage used, they were not in a range sufficient to produce suppression of the pituitary-adrenal axis in most individuals. Thus, she no longer demonstrated the lack of suppressibility characteristic of Cushing’s disease, and her response to dexamethasone would seem to have normalized.

Our patient is one of those individuals with proven Cushing’s disease who have been found to metabolize dexamethasone more slowly than control subjects, leading to higher than expected drug levels, thus causing suppression of plasma cortisol levels during standard dexamethasone testing. What remains to be explained is the cause of the apparent decreased rate of clearance of the drug. It is probably not related to the presence of Cushing’s disease itself, since only a minority of patients with the disorder appear to have this additional abnormality.

The case described here shows that a normal response to dexamethasone suppression testing in patients who are suspected of having Cushing’s disease does not necessarily exclude the diagnosis. Normal suppression responses in the face of typical clinical presentation may indicate the presence of coincident abnormal dexamethasone clearance in a patient with Cushing’s disease.

References