ORIGINAL ARTICLE

Relation Between Pre- and Post-Dexamethasone Test Cortisol Values in Cushing's Disease

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The dexamethasone test has been widely used for diagnosing hypercortisolism.
Materials and Methods: We assessed the relationship between the basal and suppressed cortisol values in urine and plasma during a low-dose dexamethasone test in patients with proved Cushing's disease.
Results: A statistically highly significant correlation was found (for urine cortisol: r = 0.66, p <0.0001; for plasma cortisol: r = 0.94, p <0.003).
Conclusion: These findings imply that the lower the pretest cortisol values, the lower are the suppressed values. In patients with suspected Cushing's syndrome and only slightly elevated cortisol excretion or low plasma concentration, the outcome might easily be considered normal. This point is particularly pertinent when assessing the post-treatment status.

Key Words: Cushing's syndrome, Adrenal cortex function test, Hypercortisolism

Introduction

Since it was introduced in 1960[1] the dexamethasone suppression test (DXM test) has been widely used when Cushing's syndrome is suspected. Though the clinical value of the test has been questioned,[2] it is still being recommended[3] and widely used. The relevant literature is extensive but in some respects difficult to interpret as varying patient definitions, steroid assays and protocols for the test have been used.[4] The classic procedure requires measurement of the urinary cortisol excretion before and during 2-3 days' DXM administration. Probably a more widely used protocol today is the "overnight test" where plasma cortisol concentration is measured in the morning, DXM given at midnight and plasma cortisol concentration measured the following morning. The two tests -as expected- will yield the same information.[5]

This study was not intended to be an audit of the value of the DXM test in patients with Cushing's disease. Its purpose was to draw attention to a point which has bearing on the interpretation of the outcome of the low dose DXM test: the relationship between the spon-

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taneous and suppressed cortisol concentrations during DXM administration.

Materials and Methods

The study was part of a national survey on patients with Cushing's syndrome (N=166).[6] There were 75 patients with Cushing's disease, i.e. caused by pituitary disease as proved from the presence of a corticotroph pituitary adenoma and/or cure after pituitary surgery as defined previously.[6]

A low dose DXM test with determination of the urinary cortisol excretion (UFC) was performed in 54 patients. Fourteen were men and 40 women, the median age being 42.0 years (range: 7.6 - 69.7). After determination of the basal 24 h urinary cortisol excretion the patients received (during hospitalisation) dexamethasone 0.5 mg orally every 6 hours for 2 days. The results from day 2 on DXM (i.e. after 48 h on DXM) will be reported. In 11 patients an "overnight" DXM test was carried out (five men, six women; median age 49.1 years, range 36.0 - 67.7). The plasma cortisol concentration was measured on day 1 at 08-09 hrs. At midnight, 1 mg DXM was given orally and another plasma cortisol determination was performed on day 2. i.e. 24 hours later. In the remaining ten patients, no DXM test was performed (the diagnosis appeared apparent with no need for additional testing) or the cortisol data could not be retrieved.

Cortisol was measured radioimmunologically. For statistical analysis the nonparametric Spearman's correlation test was used.

Results

The relationship between the UFC value, on the day just before administration of DXM was begun, and the UFC value from day 2 during DXM administration was significant ($r= 0.66$, $p <0.0001$) (Fig. 1).

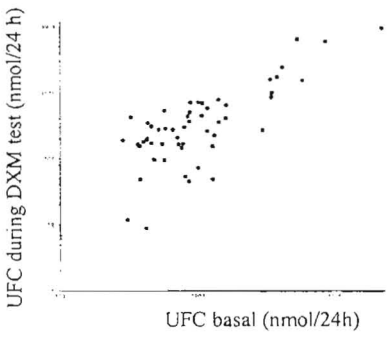

Fig. 1. Urinary excretion of cortisol (UFC) before and during dexamethasone (DXM) administration log scale

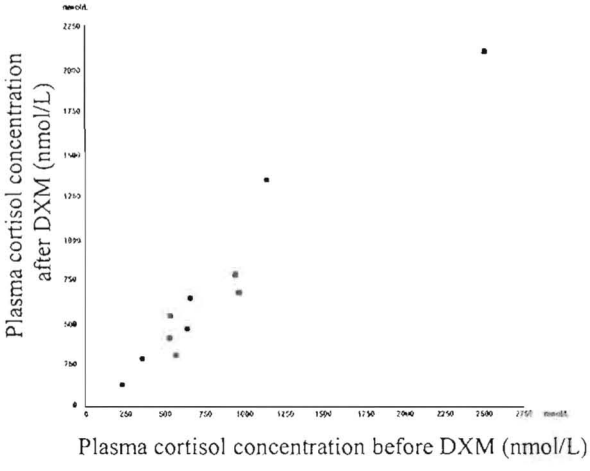

Fig. 2. Plasma cortisol concentrations before and after DXM ('over-night' DXM test)

Nadir UFC values were <40 μg/24 h (110 nmol) in nine (16.7 %), <20 (55) in five (9.8 %) and <10 (28) in two (3.9 %) patients.

The variation in the relative suppressibility [100 – ((UFCDXM/UFCbasal) × 100); where UFCDXM is the amount of cortisol excreted on day 2 of the DXM administration and UFCbasal is the basal UFC excretion] was considerable: from -32.3 (i.e. an increase in excreted cortisol) to 97.9 with a median of 58.1. There was no association between the

spontaneous amount of cortisol excreted and the relative degree of suppressibility. The association between the plasma cortisol concentrations before and after 1 mg DXM at midnight appears in Fig. 2 ($r = 0.94$, $p < 0.003$).

Discussion

The DXM test was devised at a time when the methods for measuring steroids in plasma and urine were non-specific and inaccurate, the techniques for imaging the adrenal glands were poor and ACTH could not be reliably measured.

The rationale for the low dose DXM test is that the suppressibility of ACTH to corticosteroid (and hence the concentration of circulating and urinary excretion of cortisol) is thought to be less in patients with Cushing's syndrome than in normals.[7]

Though many studies have addressed the problem of how the result of the test should interpreted there is no consensus. The wide variation in the interpretation of the short, "overnight" DXM test is attested by recent reports from the UK.[4,8] There is no agreement on what constitutes a normal outcome of the classic DXM test with determination of UFC. The upper normal limit for the suppressed UFC has been reported to be 40 µg/24 h (110 nmol),[5] 25 (69 nmol),[9] 20 (55 nmol)[10] and 10 (28 nmol).[4]

We found a highly significant relation between the urinary cortisol excretion before and during the DXM test and also between plasma cortisol concentrations before and after DXM. The association between the basal and suppressed cortisol levels has received little consideration in the published studies on the DXM test. In a previous study this relationship was found to be very close.[11] Few earlier reports on the DXM test have included the data from the individual patients. If these data[12] are calculated, a similar close relationship ($p < 0.002$) is revealed, both in patients with Cushing's disease and in normal controls. The results given by Blunt et al[13] with a higher dose of DXM also demonstrate a significant correlation between the basal and suppressed UFC values ($p = 0.01$).

Tyrrell et al[14] reported the individual plasma cortisol concentrations before and after DXM in 60 patients with proved Cushing's disease. Calculation of their data revealed a significant association ($p < 0.005$). A larger amount of DXM was given than in our study and various cortisol assays were used, some of which may not have been completely specific.

The close relationship between the basal and suppressed UFC values has practical implications. In some circumstances it may not be critical, e.g. when the diagnosis clinically is beyond doubt and/or the cortisol excretion is high. However, in patients with Cushing's disease presenting with relatively low basal UFC values, DXM may induce suppression to levels within the range often taken to reflect a normal response. In some patients with hypercortisolism, the correct diagnosis might be missed if too much reliance is given to the outcome of a DXM test.

However, in one situation this point is of major importance. It has become routine in many centers to include a DXM test when assessing the result of therapy in patients with Cushing's disease. It is clinical experience that treatment for hypersecreting pituitary adenoma (e.g. transsphenoidal surgery) often will result in a relatively low (as compared to preoperatively) secretion of the peripheral hormone -in this context cortisol. In this setting the result of a DXM test might -fallaciously- be taken to prove a successful outcome.

In conclusion, in patients with suspected hypercortisolism and a relatively low excre-

tion of cortisol (or low plasma cortisol concentration), the result of a DXM test should be interpreted with caution. These patients appear to be those in whom the DXM test theoretically might be of particular value.

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