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COMPARISON OF ORAL AND INTRAVENOUS DEXAMETHASONE SUPPRESSION TESTS IN THE DIFFERENTIAL DIAGNOSIS OF CUSHING'S SYNDROME

By

R. J. M. Croughs, R. Docter and F. H. de Jong

ABSTRACT

In seven cases of proven Cushing's syndrome, the intravenous infusion of dexamethasone at a rate of 1 mg/h for a period of 5 hours readily distinguished pituitary dependent Cushing's syndrome from other causes of Cushing's syndrome. Thus the 5 h – iv dexamethasone test may give the same differential diagnostic information as the classical oral dexamethasone suppression test of Liddle. The test is quick to perform, obviates the need for accurate urine collections and is not influenced by variations in the intestinal absorption of the glucocorticoid.

The various forms of Cushing's syndrome have several biochemical characteristics in common; they generally lack a circadian rhythm in plasma cortisol levels, and dexamethasone at a relatively low dose level fails to bring about a normal suppression of either urinary 17-OHCS or 17-OGS (Ney et al. 1968).

Once a diagnosis of Cushing's syndrome has been made, it is necessary to identify its cause. Of crucial importance in the differential diagnosis of Cushing's syndrome is the response to a high dose of dexamethasone; characteristically, in cases of pituitary dependent Cushing's syndrome, clear suppression of urinary 17-OGS will be obtained, whereas no suppression is seen in cases of Cushing's syndrome due to an adrenocortical tumour and in the ectopic ACTH syndrome (Ney et al. 1968).
The classical oral dexamethasone suppression test (Liddle 1960) is both of diagnostic and differential diagnostic value. Quantities of dexamethasone (2 mg/day for a period of two days) which profoundly suppress urinary 17-OGS excretion in normal subjects, fail to bring about such a response in patients with Cushing’s syndrome; larger quantities of dexamethasone (8 mg/day for a further period of two days) bring about clear suppression of urinary 17-OGS only in patients with pituitary dependent Cushing’s syndrome.

It has been shown that the identification of Cushing’s syndrome is also possible by the oral administration of 1 mg dexamethasone at 12 p.m. followed by measurement of the plasma cortisol levels the next morning at 8 a.m.; in cases of Cushing’s syndrome, Nichols et al. (1968) demonstrated that the 8 a.m. plasma cortisol levels were almost invariably above 10 μg/100 ml, whereas in normal subjects lower values were found in this test. Thus, the single dose oral dexamethasone suppression test gives the same information as the first part of the classical Liddle test.

The present study compares the differential diagnostic value of oral and intravenous dexamethasone tests in Cushing’s syndrome.

**Patients**

Nineteen patients with Cushing’s syndrome were investigated. A diagnosis of Cushing’s syndrome was based on the clinical picture, the absence of a diurnal rhythm of plasma cortisol and the absence of a substantial decrease in urinary 17-OGS excretion after the administration of a low dose of dexamethasone. In all the cases the degree of hypercorticism was estimated by measuring cortisol secretion rate. The more detailed diagnosis «pituitary dependent Cushing’s syndrome» was made in fifteen cases by demonstrating a suppressive effect of high doses of dexamethasone and also by demonstrating stimulation under the influence of metyrapone and lysine-vasopressin. Three patients suffered from Cushing’s syndrome due to an adrenocortical tumour while the presence of an ectopic ACTH syndrome was demonstrated in one patient. In all cases pathological examination of the adrenals was in agreement with the clinical diagnosis. Detailed clinical and biochemical information and the results of therapy in eleven patients (Table 1: Be, St, Te, Kl, Ko, Ca, Sl, Sta, Ku, Ze, Jo) are presented elsewhere (Croughs 1970; Croughs & Docter 1971; Croughs et al. 1972a,b).

**Methods**

Oral dexamethasone suppression test (Liddle 1960) was performed by oral administration of 0.5 mg dexamethasone every six hours for a period of two days, followed by a dose of 2 mg every six hours for a further two days. Urine was collected for the determination of 17-OGS over a period of eight days, starting 48 h before dexamethasone administration. Completeness of urine collection was assessed by measurement of the creatinine excretion. On the low dose of dexamethasone, nine normal

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subjects showed suppression of their urinary 17-OGS excretion to less than 8.9 mg/day on the second day (mean: 6.1 mg/day; range 3.7–8.9 mg/day).

3 h intravenous dexamethasone test was carried out under clinical conditions and started between 9.00 and 9.30 a.m. Thirty minutes after inserting an indwelling needle into a forearm vein, an infusion of dexamethasone phosphate in isotonic saline was given at a rate of 1 mg/h for 3 hours.

Blood samples for the estimation of plasma cortisol were obtained immediately before the start of the infusion and at the end of the infusion.

3 h intravenous dexamethasone test was carried out using the same precautions as in the 3 h test. An infusion of dexamethasone phosphate in isotonic saline was given at a rate of 1 mg/h for 5 hours.

Blood samples for the estimation of plasma cortisol were obtained immediately before the start of the infusion, after 3 hours and at the end of the infusion.

Plasma cortisol was measured by a modification of the method of Eechaute (1966). The fiducial range of any duplicate determination is the mean ± 2.45 μg/100 ml (P = 0.05).

For the range of plasma cortisol levels between zero and 10 μg/100 ml the fiducial range of a duplicate determination is the mean ± 1.75 μg/100 ml (P = 0.05) (Croughs 1970). In a few cases plasma cortisol was estimated by a competitive protein binding method (de Jongh & van der Molen, in press).

Cortisol secretion rate was measured by the method of Thyssen et al. (1967). Normal values are less than 30 mg/day in our laboratory. Details have been described previously (Croughs 1970).

Urinary 17-oxogenic steroids (17-OGS) were measured according to standard methods (Appleby et al. 1955).

RESULTS

Tables 1 and 2 show the results of the oral dexamethasone suppression test.

In addition, the first group of twelve patients was also submitted to the 3 h – iv dexamethasone test (Table 1), while the second group of seven patients was submitted to the 5 h – iv dexamethasone test (Table 2).

The oral dexamethasone suppression test was performed in fourteen out of fifteen patients with pituitary dependent Cushing’s syndrome (Tables 1 and 2). Using the high dose level of dexamethasone, clear suppression of urinary 17-OGS to values of less than 50% of the basal value was obtained in eleven patients; in one patient (Ke), suppression was less pronounced, while in two patients (Sti and Bo), no suppression could be demonstrated. Furthermore, no suppression was obtained in two patients with Cushing’s syndrome due to an adrenocortical adenoma, and the test was not performed in one patient with an ectopic ACTH syndrome and in one patient with Cushing’s syndrome due to an adrenocortical carcinoma.

The results of the 3 h – iv dexamethasone test are shown in Table 1. It can be seen that in most patients with pituitary dependent Cushing’s syndrome the 3 h plasma cortisol levels are below the basal values; however, almost in-
Table 1.
Oral dexamethasone suppression test and 3 h – iv dexamethasone test in patients with Cushing's syndrome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Cortisol secretion rate (mg/day)</th>
<th>Oral dexameth. test urinary 17-OGS (mg/day)</th>
<th>3 h – iv dexameth. test Plasma cortisol (µg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>basal 2nd day 2 mg 2nd day 8 mg</td>
<td>basal 3 h</td>
<td></td>
</tr>
<tr>
<td>Be</td>
<td>Pit. dep. Cush. syndr.</td>
<td>99</td>
<td>43.6 25.5 14.0</td>
<td>29.0 16.0</td>
</tr>
<tr>
<td>St</td>
<td>&quot;</td>
<td>74.5</td>
<td>33.0 23.0 11.5</td>
<td>11.3 7.8</td>
</tr>
<tr>
<td>Te</td>
<td>&quot;</td>
<td>41.9</td>
<td>25.0 17.0 11.0</td>
<td>12.4 7.3</td>
</tr>
<tr>
<td>Kl</td>
<td>&quot;</td>
<td>58.9</td>
<td>35.0 30.0 16.5</td>
<td>13.0 9.6</td>
</tr>
<tr>
<td>Ko</td>
<td>&quot;</td>
<td>54.7</td>
<td>24.5 26.2 11.8</td>
<td>23.9 7.1</td>
</tr>
<tr>
<td>Ca</td>
<td>&quot;</td>
<td>93.4</td>
<td>35.5 44.2 14.9</td>
<td>24.5 23.9</td>
</tr>
<tr>
<td>Sl</td>
<td>&quot;</td>
<td>49.2</td>
<td>not performed</td>
<td>17.1 12.5</td>
</tr>
<tr>
<td>Sta</td>
<td>&quot;</td>
<td>92.3</td>
<td>29.0 25.6 11.3</td>
<td>27.3 17.7</td>
</tr>
<tr>
<td>Sti</td>
<td>+ subtot. adr. and pit.</td>
<td>41.6</td>
<td>24.5 26.0 20.0</td>
<td>17.0 12.0</td>
</tr>
<tr>
<td></td>
<td>irr.</td>
<td></td>
<td></td>
<td>17.0 10.3</td>
</tr>
<tr>
<td>Ku</td>
<td>Cush. syndr. due to</td>
<td>53.8</td>
<td>24.1 33.6 39.0</td>
<td>16.6 15.3</td>
</tr>
<tr>
<td>Ze</td>
<td>adrenocort. adenoma</td>
<td>45.3</td>
<td>19.4 21.5 19.5</td>
<td>11.8 11.0</td>
</tr>
<tr>
<td>Jo</td>
<td>Ect. ACTH syndr.</td>
<td>209.4</td>
<td>not performed</td>
<td>47.8 46.6</td>
</tr>
</tbody>
</table>
Table 2.
Oral dexamethasone suppression test and 5 h – iv dexamethasone test in patients with Cushing's syndrome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Cortisol secretion rate (mg/day)</th>
<th>Oral dexameth. test urinary 17-OGS (mg/day)</th>
<th>5 h – iv dexameth. test Plasma cortisol (µg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>basal</td>
<td>2nd day 2 mg</td>
<td>2nd day 8 mg</td>
</tr>
<tr>
<td>Ke</td>
<td>Pit. dep. Cush. syndr.</td>
<td>105.5</td>
<td>31.0</td>
<td>34.6</td>
</tr>
<tr>
<td>Jon</td>
<td>&quot;</td>
<td>77.3</td>
<td>38.1</td>
<td>27.8</td>
</tr>
<tr>
<td>Ho</td>
<td>&quot;</td>
<td>45.0</td>
<td>22.0</td>
<td>12.3</td>
</tr>
<tr>
<td>Ga</td>
<td>&quot;</td>
<td>226.3</td>
<td>58.0</td>
<td>25.1</td>
</tr>
<tr>
<td>Bo</td>
<td>&quot;</td>
<td>114.7</td>
<td>39.3</td>
<td>40.2</td>
</tr>
<tr>
<td>Kr</td>
<td>&quot;</td>
<td>?</td>
<td>35.3</td>
<td>27.8</td>
</tr>
<tr>
<td>La</td>
<td>Adr. cort. Ca</td>
<td>?</td>
<td>not performed</td>
<td></td>
</tr>
</tbody>
</table>

* 5 mg dexamethasone infused in 3 h.
variably the values remain above 50% of the basal values. In addition, in one patient (Ca), no suppression could be demonstrated. For these reasons the test was abandoned.

The results of the 5 h – iv dexamethasone test are shown in Table 2. In the six patients with pituitary dependent Cushing’s syndrome clear suppression test a similar degree as obtained in the oral dexamethasone suppression test could be demonstrated. Furthermore, in patient Ca, a 5 h infusion with dexamethasone reduced the plasma cortisol level from 21.5 µg/100 ml to 8.8 µg/100 ml.

DISCUSSION

Since its introduction by Liddle (1960), the oral dexamethasone suppression test has been widely used. Essentially, the test serves both diagnostic and differential diagnostic purposes. A normal response to the lower dose of dexamethasone may be considered as evidence that the patient is not suffering from Cushing’s syndrome, and this obviates the need to give the higher dose; however, in actual practice, the two dose schedules are often given consecutively because of the delay in obtaining the results of the urinary steroid analyses.

The diagnostic value of the test is considerable, although both normal suppression in patients with Cushing’s syndrome and abnormal responses in normal subjects have been observed (Streeten et al. 1969; Nichols et al. 1968). Nichols et al. (1968) have shown that the single dose oral dexamethasone suppression test has at least the same diagnostic reliability. This test is very suitable for use on an out-patient basis and ultimately may prove to be the best screening test for the diagnosis of Cushing’s syndrome.

The differential diagnostic value of the Liddle test is also of great importance. Initially (Liddle 1960), it was shown, that by using the high dose of dexamethasone, suppression of the urinary 17-OHCS to values less than 50% of the basal values was obtained in patients suffering from pituitary dependent Cushing’s syndrome, whilst this degree of suppression was not obtained in patients with Cushing’s syndrome due to an adrenocortical tumour. Recently, Liddle et al. (1969) reviewed their experience with 100 patients suffering from Cushing’s syndrome. It was concluded that in 98% of cases with pituitary dependent Cushing’s syndrome, a reproducible decrease of 40% or more in urinary 17-OHCS was obtained, whereas in cases of Cushing’s syndrome due to an adrenocortical tumour, reproducible suppression was never observed. Among the patients with an ectopic ACTH syndrome, 6% showed reproducible suppression; these patients usually suffered from ACTH producing bronchial adenomas or thymomas. However, not all investiga-
tors have obtained such clear-cut findings; from a review of the literature, Nichols et al. (1968) concluded that only 82% of patients with pituitary dependent Cushing’s syndrome showed suppression of 17-OHCS to values less than 50% of the basal values. Our own observations in a limited number of cases appear to confirm this conclusion. It has been mentioned that non-suppressibility is especially found in the more severe or more chronic cases of pituitary dependent Cushing’s syndrome (Fraser 1968). Despite its limitations, the test remains of great differential diagnostic value and is a very useful guide in the selection of therapy in Cushing’s syndrome. Nevertheless, there are disadvantages in the test procedure. It requires at least five accurate consecutive 24-hour urine collections and regular administration of dexamethasone during four days; furthermore the results may be influenced by variations in the intestinal absorption of dexamethasone.

The present study was carried out in order to overcome these problems. The differential diagnostic value of the oral dexamethasone suppression test was compared with the results of the intravenous dexamethasone tests in which dexamethasone was infused at a rate of 1 mg/h for 3 or 5 hours. It could be demonstrated that in cases of pituitary dependent Cushing’s syndrome similar degrees of suppression were obtained both with the 5 h – iv dexamethasone suppression test and the oral dexamethasone suppression test; the results of the 3 h – iv dexamethasone test were less satisfactory.

Of particular interest are the observations in patients Sti and Bo. In patient Sti (Table 1) a diagnosis of Cushing’s syndrome was made elsewhere in 1955. At that time she was treated by subtotal adrenalectomy and pituitary irradiation with 3000 rad. When she was seen in our department thirteen years later, the patient showed the clinical picture of full blown Cushing’s syndrome, although the cortisol secretion rate was only moderately elevated. She responded neither to oral administration of metyrapone, nor to high doses of dexamethasone in the Liddle test; however, reproducible suppressibility could be demonstrated in the 3 h – iv dexamethasone test. No clinical signs of malabsorption were present. At operation a 5.5 g weighing hyperplastic adrenal remnant was removed from the right side.

It remains to be seen, whether decreased intestinal absorption of dexamethasone is characteristic for the non-suppressibility which may be seen in chronic cases of pituitary dependent Cushing’s syndrome.

Patient Bo (Table 2) is another example of non-suppressibility in the Liddle test, whereas suppression could be demonstrated in the 5 h – iv dexamethasone test. The plasma ACTH, as determined by radioimmunoassay decreased from 137 pg/ml to 65 pg/ml during the latter test. Detailed analysis showed that this patient suffered both from a non-ACTH secreting medullary carcinoma of the thyroid associated with chronic diarrhoea and from a pituitary dependent Cushing’s syndrome! The observations in patients Sti and Bo suggest that
so called »non-suppressibility« in pituitary dependent Cushing's syndrome is, at least in some cases, due to a decreased intestinal absorption of dexamethasone.

Thus, it appears that the 5 h – iv dexamethasone test has fundamental advantages over the oral dexamethasone test in the differential diagnosis of Cushing's syndrome. In addition, the test is more practicable and the results are obtained more quickly. In fact, the oral dexamethasone suppression test was not performed in patients Jo (Table 1) and La (Table 2), since the respective diagnoses of ectopic ACTH syndrome and Cushing's syndrome due to adrenocortical carcinoma were already highly likely on clinical grounds alone and rapid treatment was indicated. It should be mentioned that in the case of patient Jo, non-suppressibility had not been documented adequately by the 3 h – iv dexamethasone test (Table 1); however, a detailed study demonstrated beyond doubt that this patient suffered from an ACTH and calcitonin secreting medullary carcinoma of the thyroid (Croughs et al. 1972a).

The intravenous dexamethasone tests were performed previously by James et al. (1965). Dexamethasone was infused intravenously at a rate of 1 mg/h in normal subjects. After three hours, the plasma cortisol levels ranged from 23 to 37 % of the resting level at zero time. In contrast, in twelve patients with »Cushing's syndrome and adrenal hyperplasia«, the rate of fall was slower and at 3 hours the plasma cortisol values ranged from 44 to 109 % of the resting levels.

It was concluded that the test was of value in the diagnosis of Cushing's syndrome. However, the test did not arouse much interest and the single dose oral dexamethasone suppression test appears to be more useful for this purpose. In most of their patients with Cushing's syndrome, James et al. (1965) continued the dexamethasone infusion for another hour. It can be seen in Fig. 2 from their paper, that even after a 4 h – infusion with dexamethasone, only six patients showed plasma cortisol levels less than 60 % of the basal values. However, of the remaining 6 patients, adequate suppression during oral administration of high doses of dexamethasone was recorded only once; the other cases either did not respond to the oral administration of high doses of dexamethasone or no oral dexamethasone suppression test was performed. The observations of these investigators are not in contradiction with our own observations both with the 3 and 5 h – iv dexamethasone test.

In our view, a combination of the single dose oral dexamethasone suppression test and the 5 h – iv dexamethasone test may prove to be a valuable substitute for the oral dexamethasone suppression test of Liddle.

A high degree of accuracy in the differential diagnosis of Cushing's syndrome may be obtained by a combination of the 5 h – iv dexamethasone test and the lysine-vasopressin test. It has been shown previously (Croughs 1970), that the LVP-test gives at least the same information as the metyrapone test.
In general, cases of Cushing's syndrome who show both suppression during the 5 h – iv dexamethasone test and stimulation during the LVP-test can be designated as suffering from pituitary dependent Cushing's syndrome; if neither suppression nor stimulation is demonstrable, a diagnosis of pituitary dependent Cushing's syndrome can be excluded. Both tests can be carried out in a period of two days if the LVP-test is performed before the 5 h – iv dexamethasone test.

In summary, the 5 h – iv dexamethasone test has both fundamental and practical advantages over the oral dexamethasone suppression test, and its differential diagnostic usefulness can be further improved by the complementary information obtained by the LVP-test.

REFERENCES


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