ORIGINAL REPORT

Overnight Dexamethasone Suppression Test in the Diagnosis of Cushing's Disease

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Abstract- Realizing the cause of Cushing's Syndrome (CS) is one of the most challenging processes in clinical endocrinology. The long high dose dexamethasone suppression test (standard test) is costly and need an extended inpatient stay. In this study we want to show the clinical utility of the overnight 8 mg dexamethasone suppression test (DST) for differential diagnosis of CS in a referral center. Retrospectively from 2002-2005 we selected the patients of endocrinology ward in Imam hospital who were admitted with the diagnosis of Cushing syndrome and had 8 mg DST (modified test) along with classic DST. In modified test a decrease in an 8 AM serum cortisol level of 50% or more is thought to indicate suppression and we compared the results of modified test with standard test. This test had been done on 42 patients: 10 male (23%) and 32 female (76%). The mean age of patients was 31.39 (15-63), 32 with proven pituitary Cushing's disease, 7 with primary adrnal tumors and 3 with ectopic ACTH syndrome. The standard test according to 50% suppression of UFC had 90.62% sensitivity, and according to 90% suppression had 43.75% sensitivity. The sensitivity of this test was 71.85% for serum cortisol suppression. The modified test (8 mg overnight DST) had 78% sensitivity. All of these tests had 100% specificity for the diagnosis of Cushing's disease. The positive predictive vale (PPV) of all of these tests was 100%. The negative predictive value (NPV) of modified test for the diagnosis of Cushing's disease was 58.82%. In standard test the NPV of serum cortisol was 52.6%, UFC 50% had 76.9% NPV and UFC 90% had 35.7% NPV. The results of serum cortisol suppression in modified test is better than standard test. Although 50% suppression of UFC in standard test had greater sensitivity than modified test, collecting of urine is difficult, time consuming and needing hospitalization, so we advice modified test that is much simpler and more convenient instead of standard test in the first step of evaluating the cause of Cushing's syndrome in referral centers.

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Key words: Cushing disease; diagnostic tests, routine; dexamethasone

Introduction

Defining the cause of Cushing Syndrome (CS) is among the most challenging processes in clinical endocrinology. There are several biochemical testing for this purpose such as measurement of plasma adrenocorticotropin hormone (ACTH), high dose dexamethasone suppression test (HDDST), and corticotrophin-releasing hormone stimulation testing. But none of these tests has sufficient diagnostic accuracy when is used alone (1).

The most common causes of Cushing Syndrome is Cushing's disease and accounts for 60-80% of cases in most series as a result, distinction of this cause has a great role in Cushing Syndrome (2).

Aron et al. first described the overnight 8-mg dexamethasone suppression test (DST) as an alternative technique to the standard DST in differential diagnosis of Cushing syndrome (3). The overnight 8-mg dexamethasone suppression test provides two important advantages : simplicity and low cost. This overnight test does not require 24-hour urine collections and it can easily be done by single dose dexamethasone injection and in outpatient settings (4).

The total number of patients for whom this test has been done is still small and the results of these studies are different.

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In this study we want to show the clinical utility of the overnight 8-mg DST according to Tyrrell criterion to differentiate various causes of Cushing syndrome in a referral center.

Materials and Methods

In this cross-sectional study patients admitted to Imam Khomeini Hospital were included. Imam Khomeini hospital is a major referral hospital and all of the patients were admitted from other hospitals of subspecialty clinics. 96 patients between year 2002 and 2005 with the diagnosis of Cushing syndrome were admitted in Endocrinology ward of Imam Hospital.

8 mg DST had been done for 46 patients, unfortunately one of these patients died before definite diagnosis, and one of them did not appear for follow up and two of them had exogenous CS, so we had 42 patients for analysis. Those patients who did not undergo surgery had their diagnosis confirmed by pathological results or radiologic imaging.

The classic high- dose dexamethasone suppression test is done by obtaining a basal 24-hour urine collection for cortisol metabolites, administering 2 mg of dexamethasone orally every 6 hours for two days, and collecting urine for cortisol metabolites during the second day (5). In pituitary cases, the urine cortisol metabolite is suppressed to 50% or less of the basal value. In patients with the ectopic ACTH syndrome and adrenal tumors, there is generally lack of suppression (5). According to another criteria a 90% suppression in urinary free cortisol (UFC) can be considered as a positive suppression result.

In the 8 mg overnight DST, patients ingested 8 mg dexamethasone orally at 11 PM, with measurement of an 8 AM cortisol level the next day. A baseline 8 AM cortisol measurement is required. Suppression of serum cortisol level to less than 50% of baseline, suggestive of a pituitary source of ACTH rather than ectopic ACTH or primary adrenal disease.

The cortisol was measured by the cortisol RIA kit (Beckman coulter company) Intra-assay and Inter- assay coefficients of variation for serum samples were 5.8% and 9.2% respectively.

Statistical methods

For sensitivity, specificity, positive predictive value and negative predictive value the 2*2 cross tale is used, and descriptive analysis for obtaining the mean.

Results

42 patients, 10 male (23%) and 32 female (76%) underwent testing. The mean age of patients was 31.39 (15-63) year, the mean of ACTH was 68.72 (0-190).

10 patients (23.8%) had hypokalemia and 54% (23 patients) had hypertension in clinical presentations.

The final diagnosis of patients include: Cushing's disease (32 patients), primary adrenal tumors (7 patients) and 3 patients with ectopic ACTH syndrome.

The standard test according to 50% suppression of UFC had 90.62% sensitivity, and according to 90% suppression had 43.75% sensitivity.

The sensitivity of this test was 71.85% for serum cortisol suppression. The modified test (8 mg overnight DST) had 78% sensitivity (Table 1).

Because none of patients with primary adrenal tumors and ectopic ACTH syndrome had suppression with these tests, all of them had 100% specificity for the diagnosis of Cushing's disease.

The positive predictive value (PPV) of all of these tests was 100%. The negative predictive value (NPV) of modified test for the diagnosis of Cushing's disease was 58.82%. in standard test the NPV of serum cortisol was 52.6%, UFC 50% had 76.9% NPV and UFC 90% had 35.7% NPV.

Discussion

Although there are several tests to define the cause of Cushing syndrome none of them are diagnostic. The classic HDDST developed by Liddle in 1960 for defining Cushing's disease (5), but at that time the ectopic ACTH syndrome had not been described. It is demonstrated that the results of HDDST in patients with the ectopic ACTH syndrome are similar to those in patients with pituitary Cushing syndrome (6).

According to study that has been done by David C. and colleagues DST is not accurate in differential diagnosis of ACTH dependent Cushing syndrome. The diagnostic accuracy of HDDST is only 70-80% (7).

Flack et al., evaluated 118 patients (94 with Cushing's disease, 14 with primary adrenal disease and 10 with ectopic ACTH syndrome). Their study confirmed a very poor sensitivity, specificity and accuracy of the HDDST when the 50% suppression criterion was used (8).

There are several studies on newer methods such as overnight 8 mg DST to find a better and easier diagnostic test. Subsequently, Bruno et al. reported that 10 of 13 patients with confirmed pituitary disease did

Table 1. Results of the study

	Overnight 8-mg	Standard serum cortisol	Standard UFC 50%	Standard UFC 90%
The number of suppressed test in cushing's disease	25	23	29	14
Total number of patients with cushing's disease	32	32	32	32
The sensitivity of the test	78%	71.85%	90.62%	43.75%

suppress plasma cortisol by more than 50% during the overnight 8 mg DST (sensitivity, 77%) (9), whereas Tyrrell et al. observed that 55 of 60 patients with confirmed pituitary disease suppressed plasma cortisol to more than 50% of the baseline during the overnight 8 mg DST (sensitivity, 92%) (10).

Helen L, Dichek and colleagues' study showed that the overnight 8-mg DST has the sensitivity of 88% and the specificity of 57% according to tyrrell criterion (suppression of plasma cortisol of more than 50% at time combination 0800 h pre-DEX and 0800 h post-DEX), and to achieve 100% specificity of the 8 mg overnight DST with 0800 h sampling times, a greater than 80% suppression of plasma cortisol was required in their patient population, which dropped the test sensitivity to 59% (11).

Tyrrell and colleagues were done the overnight DST in hospitalized patients (10). Bruno et al did not state whether their test was done on an inpatient or outpatient basis (9).

Although in our study the specificity of standard and modified test was 100%, the number of patients with primary adrenal tumors and ectopic ACTH syndrome was not enough to have a correct judgment.

Most of the diagnostic tests used in Cushing syndrome have been developed and tested in highly specialized referral centers and in selected population (12), so all of these studies had spectrum bias that refers to the variability of diagnostic test performance across different population hence the spectrum of examined subjects, which include patients with various degrees of disease and severity and control subjects (13).

The source of ectopic ACTH secretion in studied patients is important because bronchial carcinoid tumors are greater dexamethasone suppressibility that may reflect the presence of functional glucocorticoid receptors in the tumor tissue (14).

In our study the sensitivity of modified test was greater than serum cortisol suppression in standard test. Although 50% suppression of UFC in standard test has greater sensitivity than modified test, urine collection is difficult, time consuming and needs hospitalization, so we advice this modified test which is much simpler and more convenient instead of standard test in the first step of evaluating the cause of Cushing syndrome in referral centers.

To have a correct suggestion for other centers and to eliminate the interfering options such as spectrum bias and the type of ectopic sources we should do this test in several hospitals and outpatient clinics and on greater number of patients. If further study corroborates this data, the overnight high- dose dexamethasone suppression test can replace the classic version in investigating the cause.

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