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PROS AND CONS OF DEXAMETHASONE SUPPRESSION TEST FOR SCREENING OF SUBCLINICAL CUSHING'S SYNDROME IN PATIENTS WITH ADRENAL INCIDENTALOMAS

G. Reimondo, B. Allasino, S. Bovio, L. Saba, A. Ardito, A. Angeli and M. Terzolo.

Medicina Interna I a indirizzo Endocrinologico, Dipartimento di Scienze Cliniche e Biologiche, AOU San Luigi Gonzaga, Università di Torino, Italy.

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Correspondence: G. Reimondo, MD
Dipartimento di Scienze Cliniche e Biologiche
Università di Torino
A.O.U. San Luigi
Regione Gonzole, 10
10043 Orbassano, Italy
Tel: ++011 9026292
Fax: ++011 9038655
e-mail: giuseppe.reimondo@unito.it

Address all correspondence and requests for reprints to: Giuseppe Reimondo, MD, Dipartimento di Scienze Cliniche e Biologiche, ASO San Luigi, Regione Gonzole 10, 10043Orbassano (TO), Italy.
e-mail: giuseppe.reimondo@unito.it

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ABSTRACT

The results of dexamethasone suppression tests (DST) in the screening of subclinical hypercortisolism are not readily comparable. Aim of the present study was to review the effectiveness of the overnight 1-mg DST and 8-mg DST to look for functional autonomy of clinically inapparent adrenal adenomas.

Sixty-eight consecutive patients with clinically inapparent adrenal adenomas were enrolled. All patients underwent 1-mg DST. The 8-mg DST was performed in the 11 patients who had post 1-mg DST cortisol >138 nmol/L and in 11 patients who had post 1-mg DST cortisol between 50 - 138 nmol/L. The a priori probability to have autonomous cortisol secretion was defined by the presence of at least two alterations of the HPA axis among reduced ACTH concentrations, elevated UFC or elevated midnight serum cortisol. Cortisol levels > 138 nmol/L after the 1-mg DST increases the post-test probability of adrenal functional autonomy to 55%, whereas cortisol levels <50 nmol/L reduce the post-test probability to 8%. Cortisol levels recorded after the 8-mg DST were non-significantly lower than after the 1-mg DST and all the patients with cortisol >138 nmol/L after the 1 mg DST maintained cortisol above this cut-point.

The 1-mg DST should be considered as the more effective test to detect autonomous cortisol secretion by a clinically inapparent adrenal adenoma when cortisol levels are >138 nmol/l, while cortisol levels < 50 nmol/L reduces remarkably the post-test probability of this event. The 8-mg DST seems to replicate by large the results of the 1-mg DST.

INTRODUCTION

Dexamethasone suppression tests have been extensively employed in the screening of subclinical hypercortisolism in patients with adrenal incidentalomas but the results of previous studies are not readily comparable since various amounts of dexamethasone and different thresholds of suppression have been used (1-3). To provide a standard, the NIH state-of-the-science conference panel recommended the 1-mg dexamethasone suppression test (DST) with the traditional cortisol threshold of 138 nmol/L to screen for autonomous cortisol secretion the adrenal masses characterized as adrenal adenomas (4). However, controversy in clinical practice still remains since some experts have used lower cut-points to increase sensitivity (5), in analogy with screening of overt Cushing's syndrome (6), while higher doses of dexamethasone (3 mg or 8 mg) have been used in other institutions with the aim to increase specificity (7).

This issue has relevant implications because clinically inapparent adrenal adenomas are increasingly recognized in the course of workup or treatment of conditions that are not related to adrenal diseases (4, 8). The optimal diagnostic approach to a patient who has an adrenal adenoma of incidental discovery has not been established; however, screening for subclinical Cushing's syndrome is reasonable particularly if the patient is young and has diseases potentially associated with cortisol excess. In such cases, adrenalectomy may be an option to remove an adenoma which is secreting cortisol autonomously (9-11).

Aim of the present study was to review the effectiveness of the overnight 1-mg DST and overnight 8-mg DST to look for functional autonomy of clinically inapparent adrenal adenomas.

MATERIALS and METHODS

Subjects

From January 2006 to June 2008, 68 consecutive patients with a clinically inapparent adrenal adenoma referred to our centre were enrolled. They were 23 men and 45 women, aged 28-81 years (median 58 years). According to the definition of adrenal incidentaloma (i.e. an adrenal mass detected serendipitously by an imaging work-up performed for the evaluation of unrelated diseases in patients without clear signs or symptoms suggestive of adrenal disease), exclusion criteria a priori were severe or paroxysmal arterial hypertension, hypokalemia (<3.5 mEq/L), clinical signs of hypercortisolism or hyperandrogenism, and patients with previous or current history of malignancies known to metastasize commonly in the adrenal glands (4, 12). When not histologically proven, the diagnosis of cortical adenoma rested on the following computed tomography (CT) criteria: size less than 6.0 cm, regular shape with well-defined margins, homogenous and hypodense content (13, 14). The diagnosis of adenoma was confirmed by a repeat CT scan after 6 months showing no significant increase in mass size, or change in mass density, in any patient (4, 12). Patient selection was also based on the results of an initial endocrine evaluation to exclude silent pheochromocytoma with equivocal imaging presentation, and normokalemic hyperaldosteronism (1-4, 12). None of the patients was suffering from depression or was taking any drug known to interfere with the HPA axis. No participant was receiving contraceptive or estrogen and progestin replacement therapy, or reported chronic consumption of alcoholic beverages. The study was designed in agreement with the Declaration of Helsinki and was approved by the local Ethical Committee. The patients volunteered for the study and gave their informed consent and were all hospitalized for the study.

Study protocol

During the time-span considered in this study, the patients with an incidentally discovered adrenal adenoma underwent a standardized diagnostic protocol including patient interview, complete physical examination to exclude the presence of typical symptoms or signs of overt

Cushing's syndrome, chest radiograph, standard 12-lead electrocardiogram, routine biochemical evaluation by means of standard laboratory procedures and an endocrine workup. Endocrine evaluation included measurement of serum cortisol at 2400 h (the blood drawing for midnight cortisol was obtained by venipuncture as inpatients in a nonsleeping state), 24-h excretion of urinary free cortisol (UFC), plasma adrenocorticotropin (ACTH) at 0800 h, and the overnight low-dose DST (1 mg, orally, at 2300 h with measurement of serum cortisol at 0800 h the following morning). The overnight high-dose DST (8 mg, orally, at 2300 h with measurement of serum cortisol at 0800 h the following morning) was performed in a group of 22 subjects. This group included all the patients (n=11) who did not suppress cortisol < 138 nmol/L after the 1-mg DST and 11 patients with post-DST cortisol between 50 nmol/L and 138 nmol/L, who were selected for presenting baseline characteristics (demographic and clinical data) matched to those of the 11 non-suppressor patients. Premenopausal women were studied in the early follicular phase of the menstrual cycle. Any subject with BMI >30 kg/m^2 was categorized as obese (15). Any subject with systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg, or on anti-hypertensive treatment was categorized as hypertensive (16). Diabetes mellitus was diagnosed if a subject was on insulin or hypoglycemic agents or when the subject's plasma glucose was ≥ 7.0 mmol/L at fasting in at least two samples collected in different days (17). Impaired fasting glucose was diagnosed when the subject's plasma glucose was between 6.1 and 7.0 mmol/L at fasting in at least two samples collected in different days (17).

Assays

Hormones were measured in-house with commercially available reagents. Serum cortisol was measured using competitive chemiluminescent enzyme immunoassay (Immulite 2000, DPC, Los Angeles, USA). The cross-reactivity with dexamethasone was negligible. Urinary free cortisol was measured using RIA (Sorin Biomedica, Saluggia, Italy) and was performed on extracted samples (extraction with methylene chloride in a hood; urine/methylene chloride 1:4; the recovery was 75%). This method was validated in previous experiments. Intra-assay and inter-assay

coefficients of variation were <6% and <11.5%, respectively. Plasma ACTH was measured by commercially available IRMA CT (Radim, Pomezia, Italy). Intra- and inter-assay coefficients of variation were: 4.2 and 8.0% for serum cortisol, 4.3 and 8.7% for ACTH, and 5.2 and 9.4% for UFC. Sensitivity of the methods was 5.5 nmol/l for cortisol assay and 1 pmol/l for ACTH. Hormone variables were measured in large groups of healthy subjects to determine the 3rd and 97th percentile that were used to define the reference ranges. The upper limit of normality for daily UFC excretion was set at 414 nmol/24 h and for midnight serum cortisol was set at 150 nmol/l; the lower cut-off for ACTH was 2.2 pmol/l.

Statistical analysis

Database management and all statistical analyses were performed by using the Statistica for Windows software package (Statsoft Inc., Tulsa, OK, USA). Rates and proportions were calculated for categorical data, and means and standard deviations for continuous data. Normality of data was assessed by the Kolmogorov–Smirnov test. For continuous variables, differences were analysed by means of the two-tailed Student's t-test when data were normally distributed and by using the Mann–Whitney U test for non-parametric data. Bonferroni adjustment for multiple comparisons was performed when appropriate. For categorical variables, differences were analysed by means of the χ^2 test and Fisher's exact test. Levels of statistical significance were set at $P < 0.05$. Bayesan effectiveness analysis was used to compute the positive predictive value of tests and compare testing strategies (18).

RESULTS

The CT diameter of the adrenal masses ranged from 1.0 to 6.0 cm (median 2.9 cm) and in only 7 patients (10.3%) was larger than 4.0 cm. Cortisol levels after 1-mg DST were significantly correlated to both mass size (r=0.31, p=0.01) and ACTH levels (r=-0.27, p=0.02). Twelve patients (17.6%, group A) suppress cortisol <50 nmol/L after 1-mg DST, 45 patients (66.2%, group B) had cortisol levels between 50 and 138 nmol/L and 11 patients (16.2%, group C) did not suppress cortisol <138 nmol/L. We did not observe any difference in the clinical characteristics among the three groups (Table 1).

The a priori probability to have autonomous cortisol secretion was defined by the presence of at least two alterations among reduced ACTH concentrations, elevated UFC or elevated midnight serum cortisol and was found in 25% of our series (17/68 patients, 6 of them had low ACTH and elevated midnight cortisol, 6 cases had both elevated UFC and midnight cortisol, 3 had low ACTH and elevated UFC, whereas in 2 cases three alterations were present). The occurrence of a cortisol level > 138 nmol/L after the 1-mg DST increases the post-test probability of adrenal functional autonomy to 55% (LR+ 3.6, 1.26-10 95% CI) according to the Bayesan effectiveness analysis. Conversely, cortisol levels <50 nmol/L reduce the post-test probability of adrenal functional autonomy to 8% (LR- 0.27, 0.04-1.96 95% CI). Intermediate results do not modify the pre-test probability (Figure 1).

Twenty-two patients who did not fully suppress after the 1-mg DST (11 patients with cortisol >138 nmol/L and 11 with cortisol between 50 nmol/L and 138 nmol/L) were further investigated with the 8-mg DST. Demographic and clinical characteristics of this subgroup did not differ significantly from those of the original cohort (data not shown). Cortisol levels recorded after the 8-mg DST were significantly higher in patients with cortisol > 138 nmol/L following the 1-mg DST compared to those with cortisol between 50 nmol/L and 138 nmol/L (262.3 ± 98.8 nmol/L vs. 142.7 ± 97.5 nmol/L, p=0.009). However, cortisol levels recorded after the 8-mg DST were non-significantly lower than after the 1-mg DST (Figure 2). All the patients

with cortisol >138 nmol/L after the 1 mg DST maintained cortisol above this cut-point after the 8-mg DST and only in 2 cases with cortisol between 50 nmol/L and 138 nmol/L the 8-mg DST was able to suppress cortisol below 50 nmol/L.

DISCUSSION

The concept of subclinical Cushing's syndrome has been introduced to characterize a condition of autonomous and dysregulated cortisol secretion, not fully restrained by the pituitary feedback, that may cause a mild and previously unrecognized cortisol excess in patients with clinically inapparent adrenal adenomas (19). Secretion of cortisol is distributed continuously from non-functioning adenomas to autonomous cortisol-producing adenomas. However, these adenomas may cause only a very mild cortisol excess, which is difficult to recognize with the tests currently used for screening (1-3, 7, 19, 20). It is, therefore, hardly surprising that the criteria for qualifying subclinical Cushing's syndrome remain controversial (4, 9, 20). Various diagnostic algorithms (biochemical testing procedures) have been used (1-4, 9, 10, 19, 20, 21) but they are often too complex and expensive to be applied for the endocrine work up of frequent tumours like adrenal adenomas, which may be detected serendipitously in about 4% of the patients undergoing abdominal CT (8). The overnight DST is convenient and appropriate for screening but it is still debated which cut-points and dexamethasone doses are more sound (21).

In the present study, we evaluated the effectiveness of different cortisol thresholds after the 1-mg DST to screen for functional autonomy of clinically inapparent adrenal adenomas. We also assessed whether the 8-mg DST may add significantly to the screening. It is intriguing that only a minority of patients with clinically inapparent adrenal adenomas (17.6%) displayed a complete cortisol suppression after the 1-mg DST. This may mean that cortisol secretion is autonomous in the majority of such patients or that the 50 nmol/l cut-point has a poor specificity. To test the effectiveness of the different proposed cortisol cut-off after the 1-mg DST by using Bayesan analysis we had to define a priori the probability of autonomous cortisol secretion based on observed alterations in the tests used to assess the function of the HPA axis. We acknowledge that such a definition is arbitrary, but the presence of at least two alterations of the HPA axis has been widely used in previous work (14, 22, 23, 24). Our data confirm that only a cut-point at 138 nmol/l achieves an incremental diagnostic effectiveness to detect functional adrenal autonomy. These findings put more value in specificity than sensitivity and this fits well with the general concept of screening in a roughly asymptomatic population, such as patients with clinically inapparent adrenal adenomas (6). Since the long–term consequences of the mild cortisol excess that

characterizes subclinical Cushing's syndrome have not been unequivocally defined, use of stringent criteria to diagnose this condition is recommended to reduce false positive results that may have negative psychological and economic consequences, leading to further testing or even unnecessary surgery (25). The limit of 50 nmol/L, on the other hand, reasonably excludes functional autonomy reducing remarkably the post-test probability of this event.

We have also evaluated if the 8-mg DST may give additional information to the 1-mg DST in the detection of cortisol autonomy. Thus, we have performed the high dose DST in all patients who had cortisol levels after the 1-mg DST higher than 138 nmol/l and in an equal number of patients with post 1-mg DST cortisol between 50 nmol/l and 138 nmol/l. These latter patients were included since the definition of an appropriate cut-off for the 1-mg DST remains controversial (1-4). In the vast majority of subjects the 8-mg DST confirmed the data obtained by the 1-mg DST and in some cases cortisol levels were even higher. This apparently surprising finding may be explained by the fact that autonomous cortisol secretion by an adrenal adenoma resists to dexamethasone suppression, whichever dose is used. Conversely, 1-mg dexamethasone is usually sufficient to suppress cortisol secretion by the non-adenomatous adrenal tissue that is driven by pituitary ACTH, while higher dexamethasone doses are not more effective (6, 26-30). As a matter of fact, the phenomenon of resistance to increasing doses of dexamethasone has been already observed in small groups of patients submitted to both tests (7, 31, 32). Spontaneous fluctuation of cortisol secretion over time, that has been demonstrated also in subclinical Cushing's syndrome (33), may contribute to the finding that cortisol was paradoxically higher after 8-mg than 1-mg DST.

The demonstration that the 8-mg DST did not suppress cortisol more than 1-mg DST gives further support to the view that many clinically inapparent adrenal adenomas are secreting cortisol autonomously and indeed other biochemical indexes of adrenal function were frequently altered in such patients. However, the 8-mg DST did not improve the capability to predict adrenal autonomy in our series.

To conclude, our data suggest that the 1-mg DST should be considered an effective test to detect autonomous cortisol secretion by a clinically inapparent adrenal adenoma when cortisol levels are higher than 138 nmol/l. On the other hand, demonstration of cortisol levels lower than 50 nmol/l

virtually exclude the possibility of functional autonomy. Intermediate results do not modify the pre-test probability, thus additional tests or repeated evaluation may be required since cortisol levels > 50 nmol/l may have a prognostic role for occurrence or persistence of subclinical Cushing's syndrome (34) and, in different clinical settings (osteoporotic and diabetic patients) may allow identification of cortisol-secreting adenomas (35, 36). The 8-mg DST, although evaluated only in a subset of subjects, seems to replicate by large the results of the 1-mg DST; thus, its routine use in clinical practice does not seem advisable.

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LEGENDS

Table 1: Demographic and clinical characteristics of patients stratified according to the 1-mg post-dexamethasone (DST) cortisol levels.

Figure 1: Fagan nomogram displaying the probability that a clinically inapparent adrenal adenoma secretes cortisol autonomously after a positive or negative 1-mg DST according to different cut-points.

Figure 2: Cortisol levels after 1-mg and 8-mg dexamethasone suppression test (DST).

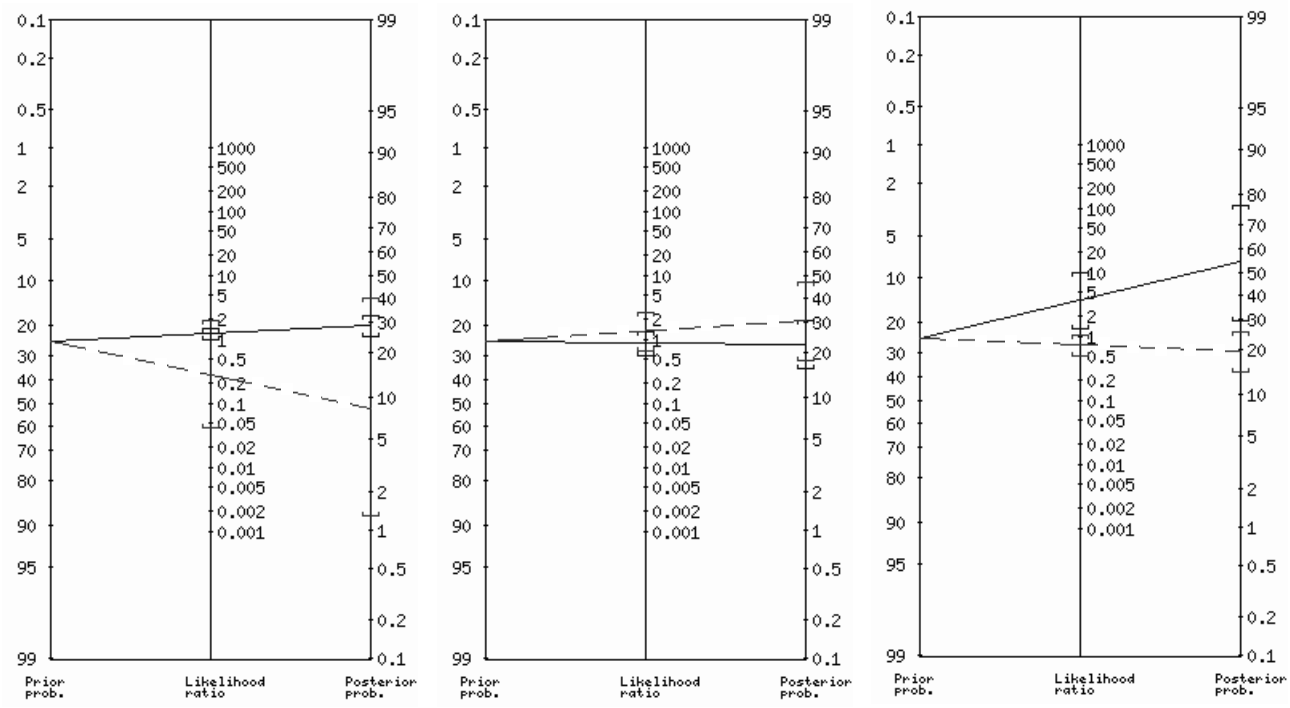
Table 1 Demographic and clinical characteristics of patients stratified according to the 1-mg post-dexamethasone (DST) cortisol levels.

	Group A (n=12)	**Group B (n=45)**	**Group C (n=11)**
Age (years, median and range)	56.5(39-63)	57.0(28-70)	58(46-73)
Hypertension (n, %)	8 (66.7%)	19 (42.2%)	5 (45.5%)
IFG/DM (n, %)	3 (25.0%)	5 (11.1%)	3 (27.3%)
Obesity (n, %)	1 (8.3%)	5 (11.1%)	1 (9.1%)

Group A: post-DST cortisol <50 nmol/L; Group B: post-DST cortisol ≥50 nmol/L and ≤ 138 nmol/L; Group C: post-DST cortisol > 138 nmol/L

Comparisons among the three groups not significant unless specified

Figure 1 Fagan nomogram displaying the probability that a clinically inapparent adrenal adenoma secretes cortisol autonomously after a positive or negative 1-mg DST according to different cut-points.



Cortisol < 50 nmol/L

Cortisol ≥ 50 nmol/L and ≤ 138 nmol/L

Cortisol > 138 nmol/L

Positive test ——————
Negative test – – – – –

Figure 2 Cortisol levels after 1-mg and 8-mg dexamethasone suppression test (DST).