The Long-Term Predictive Accuracy of the Short Synacthen (Corticotropin) Stimulation Test for Assessment of the Hypothalamic-Pituitary-Adrenal Axis

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Context: The high-dose short Synacthen (corticotropin) test (SST) is widely used to investigate suspected secondary adrenal insufficiency, but concern remains about falsely reassuring results.

Objective: Our objective was to evaluate the long-term safety of the SST.

Method: We retrospectively evaluated the clinical outcome in 178 patients who achieved 30-min cortisol values in the lowest 15th percentile of normal healthy responses. Thirty patients were later excluded because of missing case notes (20 patients) or unsubstantiated pituitary pathology (10 patients). The remaining 148 patients were divided into two groups: group 1, patients with cortisol response between the 5th and 15th percentiles of normal response (551–635 nmol/liter, 98 patients); and group 2, patients with borderline response between the 2.5th and 5th percentiles (510–550 nmol/liter, 50 patients). Patients did not receive routine glucocorticoid therapy, but those in group 2 were advised to take hydrocortisone in case of intercurrent illness.

Results: The median follow-up period from the initial SST was 4.2 yr (range, 4 months to 7 yr). A total of 137 patients showed no clinical or biochemical evidence of adrenal insufficiency during follow-up. Of the remaining 11 patients, seven became hypocortisol after subsequent pituitary surgery or radiotherapy, one patient in group 1 developed adrenal insufficiency at 2 yr, and one patient in group 2 developed adrenal insufficiency at 6 months. The other two patients who were in group 2 had clinical diagnostic uncertainty.

Conclusion: The high-dose SST is safe for the purpose of excluding clinically significant secondary adrenal insufficiency and is indicated as the first line of investigation for this purpose. (J Clin Endocrinol Metab 91: 43–47, 2006)

The choice of the most appropriate test for the assessment of the hypothalamic-pituitary-adrenal (HPA) axis has been the subject of much controversy over the last 20 yr. The insulin tolerance (hypoglycemia) test (ITT) has been traditionally regarded as the gold standard, largely because of the work by Plumpton and Besser (1), which showed that a normal cortisol response to the ITT predicts a healthy cortisol response to major abdominal surgery. The ITT, however, has several limitations; it is labor intensive, requires medical supervision, and can be hazardous particularly in young children (2) and in adults with seizure disorders or heart disease, and adequate hypoglycemia is not achieved in some cases (3). Several alternative tests for the assessment of the HPA axis have been proposed over the years but only the short Synacthen (corticotropin) test (SST) (4–6) consistently demonstrated good sensitivity and specificity when compared with the ITT in large studies (4, 5, 7–11). The test relies on the assumption that chronic corticotropin (ACTH) deficiency results in adrenal atrophy and hence hyporesponsiveness to exogenous administration of ACTH. Excellent correlation has been documented between the 30-min cortisol response to the SST and peak cortisol response to ITT (4).

Several studies, however, have reported discrepancies between cortisol responses to the SST and the ITT, raising concerns that the SST may give false reassurance because some patients who pass the SST show subnormal response to the ITT (12–17). However, the interpretation of the results of such reports is complicated by several factors including arbitrary definitions of normal cutoff responses for both the ITT and SST in some studies, variability in the analytical accuracy of the cortisol assays used, a tendency of the ITT to err on the side of caution (1), problems relating to ITT reproducibility (18), and inappropriate use of the SST in clinical situations where sensitivity of the HPA axis is rapidly changing (e.g. pituitary surgery/apoplexy within the last 3 wk) (11, 16, 19). Data from these studies are, therefore, insufficient to judge the safety of the SST, which can only be reliably derived from long-term follow-up of patients who have passed the SST and are left without glucocorticoid therapy.

Because most of the discrepancies between the SST and ITT occur in those patients who show ACTH-stimulated cortisol values in the lower range of the normal response [values in the literature between 500 and 650 nmol/liter (18 and 23 μg/dl)] (6, 7, 9–11, 17), it will be particularly interesting and clinically important to investigate the long-term clinical outcome in this subgroup of patients as it would be the obvious potential high-risk category for false negative (false reassurance) results. To address this subject, we re-
Patients and Methods

Between January 1998 and December 2004, 917 SSTs were performed in our hospital for 748 patients. In our laboratory, we previously defined the 5th percentile for a 30-min cortisol response to high-dose Synacthen in normal controls as 550 nmol/liter (19.6 μg/dl) (20), which we regard to be a clear pass not requiring any glucocorticoid replacement. In clinical practice, values between the 2.5th and 5th percentiles of the normal response [510–550 nmol/liter (18.2–19.6 μg/dl)] are interpreted to be safe for the purpose of withholding routine glucocorticoid therapy, but as a precaution, those patients are advised to take stress doses of hydrocortisone in cases of intercurrent illness. Any 30-min cortisol values less than 510 nmol/liter were interpreted as a fail response necessitating regular hydrocortisone replacement.

A 30-min cortisol of more than 510 nmol/liter was achieved in 711 SSTs for 614 patients (range, 510–1992 nmol/liter), and 178 patients achieved a 30-min response between the 2.5th and 15th percentiles of the normal response [510 and 635 nmol/liter (18.2 and 22.7 μg/dl)] and were eligible for inclusion in the study. Median basal serum cortisol concentration for the 178 patients in the study population was 298 nmol/liter (10.6 μg/dl) with a range of 134–554 nmol/liter (4.8–19.8 μg/dl) and was significantly higher (P < 0.001) than basal cortisol concentration for the 134 patients who failed the SST [157 (±20–461) nmol/liter; 5.6 (±0.7–16.5) μg/dl].

Twenty patients were excluded from the final analysis because of missing case notes. Ten patients were later excluded because they had no evidence of hypothalamic-pituitary disease, leaving 148 patients (94 females) to be included in the final analysis (Fig. 1). A 30-min cortisol response between 551 and 635 nmol/liter was achieved in 98 patients and a response between 510 and 550 nmol/liter in 50 patients. The clinical indications for the SSTs are reported in Table 1. All patients with pituitary tumors had macroadenomas except one patient who previously had successful removal of an ACTH-secreting microadenoma. All patients were followed up in our pituitary clinic at regular intervals, and clinical assessment of symptoms or signs of adrenal insufficiency and ability to cope with intercurrent illness were made and recorded in the notes. Patients who underwent pituitary surgery were treated empirically with hydrocortisone 20–30 mg/d in divided doses from the time of discharge until a postoperative SST was performed, usually 6 wk later. Although it is our policy to interrupt estrogen therapy for 6 wk before performing the SST, 23 patients were tested while on estrogen replacement therapy (19 patients) or the oral contraceptive pill (four patients). However, none of the postoperative female patients were tested on estrogen.

The SST was performed between 0900 and 1200 h by the administration of synthetic ACTH1-24 im (Synacthen 250 μg; Ciba Geigy, Basel, Switzerland). Serum samples were collected basally and at 30 min for cortisol measurements. In patients treated with hydrocortisone replacement, this was stopped for 24 h before the test. For patients with acute pituitary insult (surgery or apoplexy), the SST was delayed for at least 4 wk to allow for the HPA axis to reset to the new level of ACTH.

Samples were assayed for cortisol using a chemiluminescence immunoassay (Advia Centaur; Bayer Diagnostics, Newbury, UK) with an interassay imprecision of less than 10% for serum cortisol concentrations between 68 and 970 nmol/liter. This assay is equivalent to the previously described Bayer ACS 180 (20) using the same reagents on a larger automated platform.

Statistics

Results are expressed as median (range). The different percentiles for the 30-min cortisol response to the high-dose SST in healthy controls were defined previously (20). Analysis was made using the statistical software package STATA (version 8; College Station, TX).

Results

The median age at testing for the 148 patients included in the analysis was 41 yr (range, 15–85 yr), and the median duration of follow-up was 4.2 yr (range, 4 months to 7 yr). One hundred forty patients (95%) were followed up for longer than 1 yr. The SST was performed at a median of 6 wk (range, 4 wk to 6 months) after hypophysectomy and at a median of 41 months (range, 9 months to 20 yr) after radiotherapy. One hundred four patients had no repeat assessment, and none of them developed any feature indicative of glucocorticoid deficiency during follow-up. Fifty-four patients had repeat SSTs; the indications and outcome are shown in Table 2.

![Fig. 1. Summary of the study protocol and clinical outcome for the high-dose SST. RT, Pituitary radiotherapy; 510–635 nmol/liter is equivalent to 18.2–22.7 μg/dl.](https://academic.oup.com/jcem/article-abstract/91/1/43/2843245/1/143268432646091.png)
TABLE 1. Indications for the high-dose SST

<table>
<thead>
<tr>
<th>Indication</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary tumors treated conservatively (14 macroprolactinomas, 14 NFPA, one TSHoma)</td>
<td>29</td>
</tr>
<tr>
<td>Posthypophysectomy (48 NFPA, 13 GH-secreting adenomas, three macroprolactinomas, one ACTH-secreting adenoma, five other sellar masses)</td>
<td>70</td>
</tr>
<tr>
<td>Postadjuvant radiotherapy for pituitary lesions (13 NFPA, eight GH-secreting adenomas, three other sellar masses)</td>
<td>24</td>
</tr>
<tr>
<td>Post primary pituitary irradiation (four NFPA, one GH-secreting adenoma, one craniopharyngiomas, two nasopharyngial tumors, three primary brain tumors)</td>
<td>11</td>
</tr>
<tr>
<td>Other pituitary pathology (three empty sellae, two hypophysitis, one idiopathic hypopituitarism, one head trauma)</td>
<td>7</td>
</tr>
<tr>
<td>Recent or current pharmacological glucocorticoid therapy</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
</tr>
</tbody>
</table>

NFPA, Nonfunctioning pituitary adenoma.

Eleven of the 23 patients who were tested while receiving estrogen replacement were subsequently restested after interruption of estrogen replacement. Four had radiotherapy in the intervening period, and one of them failed the SST (32 months after radiotherapy); seven were tested routinely, and all seven patients passed. None of the remaining 12 patients showed any features of hypoadrenalism during follow-up (median, 4 yr; range, 1–7 yr).

Three patients (of the original cohort of 178 patients identified) died during the follow-up period from causes unrelated to adrenal disease; one died from congestive cardiac failure, another from a cerebrovascular accident, and the third from myocardial infarction. We ascertained that all 20 patients who were excluded because of missing case notes were alive from recent electronic records of outpatient clinic visits and communications with their family or other hospital doctors (in the preceding 6 months) or by phone contact with their family doctor. None of them were on glucocorticoid replacement, and all were well.

Patients with a cortisol response greater than 550 nmol/liter (19.6 μg/dl; n = 98)

Five patients initially passed the SST but were found later to be hypoadrenal, four after repeat pituitary surgery or radiotherapy and all four were asymptomatic. The clinical history of the fifth patient follows.

Case history 1. A 32-yr-old woman was found to have an empty sella during investigations of secondary amenorrhea and infertility. SST carried out at 0900 h showed a cortisol rise from 189 to 560 nmol/liter (6.8 to 20 μg/dl). In addition to gonadotropin deficiency, she also had TSH deficiency and low IGF-I levels. She became pregnant with ovulation induction and had an uneventful pregnancy and labor. She was well until 9 months postpartum when she started to complain of tiredness. A repeat SST (2 yr after initial test) showed a basal cortisol of 92 nmol/liter (3.3 μg/dl) rising only to 162 nmol/liter (5.8 μg/dl).

Patients with a cortisol response between 510 and 550 nmol/liter (18.2–19.6 μg/dl; n = 50)

Six patients who initially achieved a response between 510 and 550 nmol/liter were later found to have a response less than 510 nmol/liter [range, 30–476 nmol/liter (1.1–17 μg/dl)], three after repeat pituitary surgery or radiotherapy, and all three were asymptomatic. The case histories of the remaining three patients follow.

Case history 2. A 53-yr-old man had SST 8 wk after transphenoidal resection of a nonfunctioning pituitary macroadenoma that showed a cortisol rise from 173 to 541 nmol/liter (6.2 to 19.3 μg/dl). Six months later, he was admitted to hospital unwell with lower respiratory tract infection and was also found to have a serum sodium of 130 nmol/liter (normal, 135–145 mmol/liter). He failed a repeat SST that showed a basal cortisol of 240 nmol/liter (8.6 μg/dl) and a 30-min cortisol of 413 nmol/liter (14.8 μg/dl). He responded well to hydrocortisone replacement.

Case history 3. A 39-yr-old woman was found to have magnetic resonance imaging evidence of a small pituitary infarct after a balloon occlusion of the internal carotid artery to treat an ophthalmic artery aneurysm. SST was performed 4 wk later and showed a rise of cortisol from 416 to 534 nmol/liter (14.9 to 19.3 μg/dl). Other pituitary hormone evaluation was normal. She had a repeat SST 6 months later that showed a cortisol rise from 392 to 476 nmol/liter (14 to 17 μg/dl). The patient was asymptomatic. She was commenced on hydrocortisone 5 mg twice daily, but she stopped the treatment herself afterward because of weight gain and lack of benefit. She has remained well since.

Case history 4. A 24-yr-old woman had the SST 6 wk after hypophysectomy for a nonfunctioning pituitary adenoma, which showed a basal cortisol of 516 nmol/liter (18.4 μg/dl) and a 30-min cortisol of 525 nmol/liter (18.5 μg/dl). She had gonadotropin, TSH, and vasopressin deficiencies and low serum IGF-I concentration. The nature of the SST response raised the clinical suspicion that the patient may have taken hydrocortisone before the test, and because the patient had severe pituitary failure, it was decided to treat with hydrocortisone as a precaution. A repeat SST, 3 yr later, showed an

### Table 2. Indications and outcome for repeat SST (cortisol response refers to 30-min ACTH$_{1-24}$-stimulated value)

<table>
<thead>
<tr>
<th>Indication for repeat SST</th>
<th>Cortisol response &gt; 550 nmol/liter (19.6 μg/dl)</th>
<th>Cortisol response 510–550 nmol/liter (18.2–19.6 μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Fail</td>
</tr>
<tr>
<td>Repeat hypophysectomy</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Routine follow-up</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms of hypoadrenalism</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>5</td>
</tr>
</tbody>
</table>
undetectable basal cortisol with a rise to 30 nmol/liter (1.1 µg/dl) after stimulation.

Discussion

Our results show that the high-dose SST performs well in clinical practice to exclude secondary adrenal suppression with very low false negative (false reassurance) results. Among patients with hypothalamic-pituitary disease and possible ACTH deficiency, who achieved a clear pass (30-min cortisol > 550 nmol/liter), only one patient (case 1) was found 2 yr later to have adrenal insufficiency in a clinical setting suggestive of evolving hypopituitarism because the patient was quite well for the 2 yr after the initial SST. Even among the patients who achieved borderline results (30-min cortisol value between 510 and 550 nmol/liter) that were deemed to be safe for the purpose of withholding routine hydrocortisone treatment, we were able to demonstrate convincingly only one case (case 2) where a patient later presented with clinically significant glucocorticoid deficiency under stressed conditions. This patient had been advised to take stress-dose hydrocortisone in case of intercurrent illness, but he failed to comply. In case 3, although the patient clearly failed the repeat SST, it is unlikely that she had clinically significant hypoadrenalism considering the absence of other pituitary hormone deficiencies, a healthy basal cortisol concentration, and the lack of benefit from hydrocortisone treatment. In case 4, a basal cortisol of 516 nmol/liter would suggest intact adrenal function (4, 19), but when the biochemical and the clinical pictures were considered carefully, hypoadrenalism was thought likely and the patient was treated. The last two cases illustrate clearly that the SST, as with any other test, should be interpreted judiciously, taking into consideration the clinical picture and also the basal cortisol concentration. Taking clinical outcome as the gold standard measure, the SST gives a false reassurance rate of less than 1%.

The cortisol assay used in this study was equivalent to the previously described Bayer ACS 180 assay that was used in a previous study to define normative responses to the SST (20) because subsequent reanalysis of the samples from the original study (20) using the current assay showed similar results. However, we would acknowledge that reanalysis of the samples from the original study could have introduced a slight bias because the samples were not fresh, and repeating the original study of 100 Synacthen tests in healthy subjects (20) was deemed not feasible. However, for the purpose of clinical decision making, we feel the cutoffs that we used are appropriate.

Only one previous study has evaluated the long-term safety of the high-dose SST with reference to clinical outcome. Gleeson et al. (21) examined the outcome of 63 patients who passed a posthypophysectomy SST and were followed up for a median of 3 yr (range, 1–10 yr). They reported the predictive value of the SST to exclude ACTH deficiency to be 97% (two patients initially passed the SST but were found to be ACTH deficient within 12 months without repeat surgery or radiotherapy), and only one patient was symptomatic. Our findings in this study corroborate their conclusion that the SST is safe for assessment of ACTH deficiency.

There have been numerous studies that attempted to establish the sensitivity and the specificity of the SST with reference to the ITT as the gold standard, and those with large sample size reported the sensitivity of the SST to be between 65 and 100% (4, 9–12, 22). The conflicting data are not surprising for several reasons. The pass cutoff for both the ITT and the SST were arbitrarily defined in most studies. The ITT tends to err on the side of caution because it has been shown that some patients who failed the ITT will show healthy cortisol response during major surgery (1), hence, failing the ITT does not always signify adrenal insufficiency. In addition, peak cortisol reproducibility of the ITT in hypopituitary patients has been shown to be poor with a 41% within subject variability (18). Even if we overlook all these limitations and accept the ITT as the gold standard reference test, most of the studies have shown that the false reassurance rate of the SST (number of false negative results as a proportion of the total number of patients studied) is low at less than 4% (10). Although it is possible that mild or borderline cases of adrenal insufficiency could occasionally be missed by the SST, the clinical significance of this entity particularly with regard to the risk of adrenal crises during intercurrent illnesses remains unknown, and it is prudent to advise the use of stress doses of hydrocortisone under stress conditions when the response to the test is borderline normal as we do in our unit.

As in our study, there have been occasional case reports of patients initially passing the SST but later presenting with symptomatic hypoadrenalism (17, 21). However, no patient has suffered long-term harm as the result, and indeed, repeat SSTs when the patients were symptomatic diagnosed secondary hypoadrenalism. Even the ITT misses secondary adrenal failure occasionally (9, 23). These sporadic reports highlight the need to maintain clinical vigilance and to make patients aware of the symptoms and signs of adrenal insufficiency so that assessment can be repeated if necessary.

Over the last few years, the low-dose (1 µg) SST was proposed as a more a sensitive alternative to the high-dose SST by some authors using the ITT or metyrapone as the reference tests (13, 24). However, these reports were not confirmed by other studies (9, 11) and a recent metaanalysis showed the two doses to have similar diagnostic utility (25). The low-dose SST is less practical than the high-dose SST and is prone to dosing errors because it requires the dilution of the 250-µg vials.

Clinicians need to be aware of certain caveats associated with the SST. The test should not be performed in the early period after an acute pituitary insult such as surgery or apoplexy (11, 16, 19), to allow sufficient time for the adrenal to involute (at least 3 wk). Defining normality should be based on the 30-min cortisol response rather than by using delayed (60-min) or incremental responses (4). The cutoff for normality is assay dependent, and therefore it should be determined in each unit from responses in healthy subjects (20). In addition, basal morning cortisol concentration should be taken into consideration because it may be reasonable to avoid routine glucocorticoid therapy in patients with a basal cortisol level of more than 400 nmol/liter (4, 19) even if they technically fail the SST but advise stress doses of hydrocortisone in cases of intercurrent illness. Conversely, caution should be exercised when the test is normal but basal morn-
ing cortisol concentration is low or low-normal as was the case in our patient described in case history 2. Repeat testing may be indicated in these situations when the results are equivocal or borderline. Concern about possible allergic reaction to synthetic ACTH has been raised, and the product data sheet advises against the use of the SST in asthma patients. However, in the absence of reliable data demonstrating allergic reactions to synthetic ACTH, it has been the policy of our unit to continue to use the SST in patients with asthma and obstructive airways disease, and in over 5000 tests performed over more than 20 yr, we have yet to see an anaphylactic event. We would argue that the SST is still safer than the ITT in this patient subgroup. Because estrogen treatment causes an increase in cortisol-binding globulin production resulting in higher serum total cortisol concentration, withdrawal of estrogen is necessary before testing cortisol reserves.

Whether there is a need for additional refinements in the definition of an adequate response in particular subgroups, such as hospitalized patients, intensive therapy patients, and the elderly/children and in the context of primary adrenal failure remains to be established.

In conclusion, the high-dose SST is reliable for the purpose of excluding clinically significant secondary adrenal insufficiency. Our experience suggests that, for the purpose of clinical decision making, true false negative (false reassurance) results are rare. With the added advantage of simplicity, low cost and labor, and lack of side effects, it should be used as the first line of investigation in suspected cases of secondary adrenal insufficiency.

Acknowledgments

Received May 19, 2005. Accepted October 17, 2005.

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