Day 5 Morning Serum Cortisol Predicts Hypothalamic-Pituitary-Adrenal Function after Transsphenoidal Surgery for Pituitary Tumors

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BACKGROUND: Adrenal insufficiency is a complication of transsphenoidal surgery (TSS) for pituitary adenoma, and correct identification of patients requiring glucocorticoid replacement is important. Controversy exists over which early postoperative 9 AM cortisol concentration reliably predicts hypothalamic-pituitary-adrenal (HPA) axis reserve, as defined by the insulin tolerance test (ITT).

METHODS: Data were reviewed for 36 patients undergoing TSS followed by day 5 postoperative 9 AM cortisol measurement and ITT 6 weeks postsurgery. All patients received postoperative glucocorticoid replacement, which was discontinued if the 9 AM serum cortisol was >300 nmol/L.

RESULTS: Of 23 patients who failed the ITT (peak cortisol ≥500 nmol/L), 20 also had a day 5, 9 AM serum cortisol <300 nmol/L. Nine of 13 patients who passed the ITT had a day 5, 9 AM cortisol >300 nmol/L. The cutoff cortisol concentration of 300 nmol/L had 86.9% (66.4%–97.2%) diagnostic sensitivity, 69.2% (38.6%–90.9%) diagnostic specificity, and 83.3% (61.8%–94.5%) positive predictive value (PPV) for detecting secondary adrenal insufficiency. Increasing the cutoff to 392 nmol/L resulted in 100% (85.2%–100%) sensitivity, 46.1% (19.2%–74.9%) specificity, and 76.6% (57.3%–89.4%) PPV. Decreasing the cutoff to 111 nmol/L resulted in 100% (75.3%–100%) specificity and 100% (67.9%–100%) PPV, although sensitivity was 47.8% (26.8%–69.4%).

CONCLUSIONS: A day 5 post-TSS 9 AM serum cortisol <111 nmol/L reliably detects secondary adrenal insufficiency, and concentrations >392 nmol/L support intact HPA function. Because concentrations of 111–392 nmol/L are poorly predictive of HPA function, glucocorticoid replacement should continue in such cases until definitive testing is performed using an ITT.

Transsphenoidal surgery (TSS)3 is an effective treatment for pituitary adenomas and offers the potential for cure (1). However, adrenal insufficiency secondary to the disruption of pituitary function is a well-recognized complication of TSS. Therefore postoperative biochemical evaluation of the integrity of the hypothalamic-pituitary-adrenal (HPA) axis is imperative (2).

A 9 AM serum cortisol measurement is routinely used to assess the integrity of the HPA axis in the early post-TSS period (3). Because only a single blood sample is required, the relative ease with which the test can be performed has made it a popular tool in assessing the integrity of the HPA axis. The insulin tolerance test (ITT) is widely regarded as the gold standard assessment of HPA-axis integrity (4–6). The ITT is considered highly reliable at detecting adrenal insufficiency, with only rare cases of adrenal insufficiency reported to be associated with a normal response (7). The test relies on potent upregulation of HPA activity and cortisol secretion in the presence of hypoglycemia. However, the physiological stress associated with hypoglycemia during ITT confers a risk of morbidity and mortality and involves significant patient discomfort (8). The use of ITT is also contraindicated in elderly patients and patients with cardiovascular disease or epilepsy (4). In light of its associated risks, performing ITT is not appropriate during the first few postoperative days, and most centers delay the ITT until 4–6 weeks after TSS (2, 6).

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Nonstandard abbreviations: TSS, transsphenoidal surgery; HPA, hypothalamic-pituitary-adrenal; ITT, insulin tolerance test; PPV, positive predictive value.

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Controversy still exists over the 9 AM serum cortisol value that most reliably predicts an intact HPA axis after TSS. Correct identification of patients who may or may not require glucocorticoid replacement is vital after TSS because a lack of glucocorticoids may be life threatening, but unnecessary exposure to therapy can be harmful. Until definitive testing of the HPA axis is performed, the initial decision to continue glucocorticoid replacement is routinely based on the value of a 9 AM serum cortisol concentration in the early postoperative period (3).

Numerous algorithms have been recommended to ensure that those patients with a normal HPA axis are not unnecessarily treated with glucocorticoids and to select those requiring dynamic testing of HPA axis function. It is widely accepted that patients with a morning serum cortisol concentration <100 nmol/L in the early post-TSS period should receive a standard maintenance of glucocorticoids, because they are at high risk of secondary adrenal insufficiency (9–13). Those patients with serum cortisol concentrations of 80–250 nmol/L are generally considered to be deficient in adrenocorticotrophin and given glucocorticoid replacement until definitive testing of HPA axis is performed (9–11, 13). In contrast, little consensus exists regarding glucocorticoid management in patients with a 9 AM serum cortisol concentration >250 nmol/L post-TSS. It has been suggested that it is safe to withhold routine glucocorticoid replacement in those patients with a morning serum cortisol of >250 nmol/L in the early post-TSS period until provocative testing of the HPA axis is performed (9–11, 13). After TSS all patients received standard glucocorticoid replacement (hydrocortisone 20 mg AM, 10 mg 12 PM, and 10 mg midafternoon). Glucocorticoid replacement was stopped 18 h before measurement of 9 AM serum cortisol concentrations and are continued on glucocorticoid replacement until dynamic testing of the integrity of the HPA axis is carried out 6 weeks after TSS. The aim of this study was to investigate in patients with pituitary adenoma the correlation between day 5 postoperative 9 AM serum cortisol concentrations and results of week 6 postoperative dynamic HPA assessment with ITT.

Materials and Methods

We reviewed retrospective data from all patients who underwent TSS for a pituitary adenoma followed by a 9 AM serum cortisol determination 5 days after TSS and an ITT 6 weeks later at Charing Cross Hospital, London, UK, during the period 2001–2008. Nine patients were identified as having Cushing syndrome and were excluded. A total of 36 patients completed all aspects of the protocol. Patient characteristics and details of underlying diagnoses are provided in Table 1.

After TSS all patients received standard glucocorticoid replacement (hydrocortisone 20 mg AM, 10 mg 12 PM, and 10 mg midafternoon). Glucocorticoid replacement was stopped 18 h before measurement of 9 AM serum cortisol 5 days after TSS. Glucocorticoid replacement (hydrocortisone 10 mg AM, 5 mg 12 PM, and 5 mg midafternoon) was continued if the morning cortisol was 300 nmol/L, but discontinued if >300 nmol/L. All patients were readmitted 6 weeks after TSS for an ITT performed using an established protocol (4–6). Patients fasted overnight then were administered intravenous insulin (0.1–0.15 U/kg) until symptomatic hypoglycemia was achieved. Blood was sampled for serum glucose and cortisol at 0, 30, 60, 90, and 120 min after insulin injection. Serum cortisol was measured by use of the Immulite 2000 cortisol assay (Siemens Medical Solutions Diagnostics). In our laboratory the functional sensitivity of the cortisol assay used with Siemens reagents was <27 nmol/L. CVs for the assay were as follows: cortisol 98 nmol/L, 9.2%; cortisol 347 nmol/L, 6.9%; cortisol 925 nmol/L, 5.6%. A peak cortisol of 500 nmol/L during the ITT was considered a sufficient cortisol response to indicate an intact HPA axis (6).

| **Table 1. Characteristics of study patients.** |
|------------------|------------------|
| **Characteristic** | **Value**        |
| Number of patients | 36               |
| Number of males   | 22               |
| Mean age, years   | 44 (range 19–69) |
| Ethnicity, n (%)  |                  |
| Caucasian         | 23 (63.9)        |
| Indian            | 8 (22.2)         |
| Afro-Caribbean    | 2 (5.6)          |
| Other/mixed ethnicity | 3 (8.3)  |
| Underlying diagnosis, n (%) |      |
| Nonsecreting adenoma | 13 (36.1)  |
| Somatotroph adenoma | 12 (33.3)  |
| Gonadotroph adenoma | 4 (11.1)    |
| Rathke’s cyst     | 3 (8.3)          |
| Thyrotrh adenoma  | 1 (2.7)          |
| Mixed somatotroph/factotroph adenoma | 1 (2.7) |
| Meningioma        | 1 (2.7)          |
| Necrotic tumor    | 1 (2.7)          |
| Pituitary masses with diameter >10 mm (%) | 23 (63.9) |
Diagnostic sensitivity was defined as the number of patients with a day 5 postoperative serum cortisol correctly identifying secondary adrenal insufficiency, divided by the total number of patients with secondary adrenal insufficiency. Diagnostic specificity was defined as the number of patients with a day 5 postoperative serum cortisol correctly excluding adrenal insufficiency, divided by the total number of patients with adequate adrenal reserve. Positive predictive value (PPV) was defined as the number of patients with a day 5 postoperative serum cortisol correctly identifying adrenal insufficiency, divided by the total number of patients with a day 5 postoperative serum cortisol indicating adrenal insufficiency, whether correctly or not. We calculated 95% CIs for specificity, sensitivity, and PPV.

**Results**

After TSS, 9 AM serum cortisol concentrations ranged from 27–607 nmol/L, and peak cortisol concentrations during ITT 6 weeks after TSS ranged from 27–971 nmol/L. A total of 23 patients failed the ITT (peak serum cortisol <500 nmol/L) and had 9 AM post-TSS serum cortisol concentrations ranging from 30–392 nmol/L. Twenty of these patients had a post-TSS 9 AM serum cortisol concentration indicating secondary adrenal insufficiency according to a 9 AM serum cortisol cutoff value of 300 nmol/L. However, the remaining 3 patients who failed their ITT had post-TSS 9 AM serum cortisol concentrations of >300 nmol/L, (322, 353, and 392 nmol/L, Fig. 1).

Thirteen patients passed the ITT (peak serum cortisol >500 nmol/L) and had post-TSS 9 AM serum cortisol concentrations ranging from 111–607 nmol/L. Nine of these patients had a post-TSS 9 AM serum cortisol concentration >300 nmol/L, suggestive of an intact HPA axis. The remaining 4 patients demonstrated a post-TSS 9 AM serum cortisol <300 nmol/L (111, 123, 224, and 245 nmol/L) suggestive of secondary adrenal insufficiency but passed their ITT 6 weeks after TSS (Fig. 1).

Overall, 29 patients had a post-TSS 9 AM serum cortisol concentration that accurately predicted the in-
tegrity of the HPA axis when this was assessed by use of an ITT 6 weeks after TSS. A total of 7 patients had a 9 AM serum cortisol concentration that did not correlate with their response during an ITT.

The diagnostic sensitivity, specificity, and PPV for individual post-TSS 9 AM serum cortisol concentrations to predict the integrity of the HPA axis based on the results of an ITT 6 weeks after TSS are shown in Table 2. The use of a post-TSS 9 AM serum cortisol concentration of <300 nmol/L to diagnose secondary adrenal insufficiency led to a sensitivity of 86.9% (95% CI 66.4%–97.2%) and a specificity of 69.2% (95% CI 38.6%–90.9%) with a PPV of 83.3% (61.8%–94.5%). The highest post-TSS 9 AM serum cortisol concentration observed in the subgroup that failed the ITT was 392 nmol/L. Increasing the post-TSS 9 AM serum cortisol cutoff to 392 nmol/L to diagnose secondary adrenal insufficiency resulted in 100% (85.2%–100%) sensitivity, and a PPV of 76.6% (57.3%–89.4%), but compromised the specificity (46.1%, 19.2%–74.9%). The lowest post-TSS 9 AM serum cortisol concentration in the subgroup that passed the ITT was 111 nmol/L. Although a reduction in the post-TSS 9 AM serum cortisol cutoff to 111 nmol/L resulted in 100% (85.2%–100%) sensitivity, and a PPV of 76.6% (57.3%–89.4%), but compromised the specificity (46.1%, 19.2%–74.9%). The lowest post-TSS 9 AM serum cortisol concentration in the subgroup that passed the ITT was 111 nmol/L. Although a reduction in the post-TSS 9 AM serum cortisol cutoff to 111 nmol/L resulted in 100% (75.3%–100%) specificity and 100% (67.9%–100%) PPV, the sensitivity was only 47.8% (26.8%–69.4%). An ROC analysis of the detection of adrenal insufficiency by post-TSS cortisol measurement revealed an area under the curve of 0.84 (95% CI 0.72–0.97) (Fig. 2).

**Discussion**

Debate is ongoing regarding which post-TSS 9 AM cortisol concentration ensures that patients with secondary adrenal insufficiency are not misdiagnosed. Watts et al. used a 3–4-day post-TSS 9 AM cortisol concentration of >250 nmol/L to permit safe withdrawal of replacement glucocorticoids pending further HPA assessment (11). Furthermore, Auchus et al. suggested that a 9 AM cortisol 3 days after TSS of >250 nmol/L was highly predictive of a normal response to a subsequent ITT (9). In our study, lowering the post-TSS 9 AM cortisol cutoff concentration to 250 nmol/L would have missed 7 of 36 (19.4%) of patients later shown to have secondary adrenal insufficiency as defined by ITT. Hagg et al. proposed that a 9 AM cortisol concentration >300 nmol/L excluded adrenal insufficiency as assessed by ITT (14). Our data suggest that a post-TSS 9 AM cortisol concentration >300 nmol/L predicts secondary adrenal insufficiency (diagnostic sensitivity 86.9% and positive predictive value 83.3%) and avoids unnecessary glucocorticoid replacement (69.2% diagnostic specificity) in most but not all cases.

The highest post-TSS 9 AM serum cortisol concentration observed in patients with subnormal response to ITT was 392 nmol/L. This result is comparable to a report suggesting that a 9 AM cortisol concentration of >400 nmol/L is highly indicative of a

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**Table 2. Diagnostic sensitivity, specificity and positive predictive values for day 5, 9 AM serum cortisol cutoff concentrations with respect to detection of adrenal insufficiency as defined by peak cortisol <500 nmol/L during ITT.**

<table>
<thead>
<tr>
<th>Detection of adrenal insufficiency</th>
<th>300 nmol/L day 5 serum cortisol cutoff</th>
<th>392 nmol/L day 5 serum cortisol cutoff</th>
<th>111 nmol/L day 5 serum cortisol cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>86.9 (66.4–97.2)</td>
<td>100 (85.2–100)</td>
<td>47.8 (26.8–69.4)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>69.2 (38.6–90.9)</td>
<td>46.1 (19.2–74.9)</td>
<td>100 (75.3–100)</td>
</tr>
<tr>
<td>Positive predictive value (95% CI)</td>
<td>83.3 (61.8–94.5)</td>
<td>76.6 (57.3–89.4)</td>
<td>100 (67.9–100)</td>
</tr>
</tbody>
</table>

**Fig. 2.** ROC curve for detecting adrenal insufficiency with day 5 postoperative serum cortisol (solid line), shown with reference line (dotted). Area under the curve is 0.84 (95% CI 0.72–0.97).
normal response to subsequent hypoglycemia (13). Many groups have suggested that a post-TSS 9 AM cortisol concentration of <100 nmol/L accurately predicts adrenocorticotrophin deficiency, thus obviating the need to perform an ITT (11, 13–14). Our results show that all patients with a post-TSS 9 AM cortisol concentration of <111 nmol/L have secondary adrenal insufficiency according to the results of their ITT. We therefore suggest that day 5 post-TSS 9 AM cortisol concentrations <111 nmol/L accurately predict adrenal insufficiency, and concentrations >392 nmol/L accurately indicate HPA axis reserve.

In our study, post-TSS 9 AM cortisol concentrations between 111–392 nmol/L correlated poorly with the results of the ITT performed 6 weeks after TSS. Pavord et al. found that 14% of patients with a 9 AM cortisol concentration between 300–399 nmol/L had a subnormal response during an ITT (13). In comparison, 3 (43%) of the 7 patients in our study with cortisol concentrations between 300–399 nmol/L showed a subnormal response to ITT. We therefore recommend that patients with day 5 post-TSS 9 AM cortisol concentrations between 111–392 nmol/L should be treated with maintenance glucocorticoid treatment and undergo dynamic testing 6 weeks postoperatively. It has been argued that the use of an even higher day 5 morning cortisol threshold of 450–500 nmol/L would avoid missing any cases of adrenal insufficiency (11, 13). A disadvantage of this approach, however, is the increased probability of unnecessary treatment with glucocorticoids.

It is interesting to consider what factors may have contributed to the disagreement in the literature regarding detection of adrenal insufficiency by a post-TSS serum cortisol measurement. It is difficult to comment on whether the day of serum sampling affects this relationship, because all studies to date have measured serum cortisol between postoperative days 3 to 7 (9, 10–11). Although Courtney et al. measured serum cortisol on both 6 and 7 days postoperatively, they did not examine differences between these measurements and those performed 2 days postoperatively (10). Our study and previous studies all employed various forms of an immunoassay technique. Assay differences may have therefore contributed to variability in cortisol cutoffs suggested in the literature (9–13). Additionally, a large fraction of the immunoreactivity detected in these assays is attributable to cortisol metabolites rather than cortisol itself (15). It is therefore important to recognize that more specific assay techniques such as mass spectrometry are likely to have different optimum cortisol cutoffs.

We conclude that a post-TSS 9 AM cortisol concentration of >392 nmol/L accurately predicts HPA axis integrity, and in these patients glucocorticoid therapy can be safely withdrawn, and further definitive testing 6 weeks after TSS is unnecessary. Similarly, a post-TSS 9 AM cortisol concentration of <111 nmol/L accurately predicts secondary adrenal insufficiency, thus permitting the continuation of glucocorticoid therapy without the need for further testing. However, on day 5 after TSS, 9 AM cortisol concentrations between 111–392 nmol/L are poorly predictive of secondary adrenal insufficiency. In such cases, glucocorticoid replacement should be continued until dynamic testing with ITT can be safely performed.

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