

The short Synacthen (corticotropin) test can be used to predict recovery of hypothalamo-pituitary-adrenal axis function.

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Abstract

Context: The 250µg Short *Synacthen* (corticotropin) Test (SST) is the most commonly used tool to assess hypothalamic-pituitary-adrenal (HPA) axis function. There are many potentially reversible causes of adrenal insufficiency (AI), but currently no data to guide clinicians as to the frequency of repeat testing or likelihood of HPA axis recovery.

Objective: To use the SST results to predict recovery of adrenal function.

Design: A retrospective, analysis of data from 1912 SSTs.

Patients: 776 patients with reversible causes of AI were identified who had at least two SSTs performed. A subgroup analysis was performed on individuals previously treated with suppressive doses of glucocorticoids (n=110).

Main outcome measures: Recovery of HPA axis function.

Results: SST 30-minute cortisol levels above or below 350nmol/L (12.7µg/dL) best predicted HPA axis recovery (AUC ROC=0.85; median recovery time 334 vs. 1368 days, $p=8.5 \times 10^{-13}$). 99% of patients with a 30-minute cortisol >350nmol/L recovered adrenal function within 4-years, compared with 49% in those with cortisol levels <350nmol/L. In patients exposed to suppressive doses of glucocorticoids, delta cortisol (30-minute - basal) was the best predictor of recovery (AUC ROC = 0.77; median recovery time 262 vs. 974 days, $p=7.0 \times 10^{-6}$). No patient with a delta cortisol <100nmol (3.6µg/dL) and a subsequent random cortisol <200nmol/L (7.3µg/dL) measured approximately 1-year later recovered HPA axis function.

Conclusions: Cortisol levels across an SST can be used to predict recovery of AI and may guide the frequency of repeat testing and inform both clinicians and patients as to the likelihood of restoration of HPA axis function.

Précis: In patients with reversible causes of adrenal insufficiency, a 30-minute cortisol level of >350nmol/L (12.7µg/dL) during a short *Synacthen* (corticotropin) test conveys a 99% chance of HPA axis recovery within 4-years.

Introduction

Adrenal insufficiency (AI) is a life-threatening condition with an established increase in morbidity and mortality (1-3) that is characterized by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and / or mineralocorticoids (4).

AI has classically been subdivided into primary (conditions directly impacting upon adrenal function, such as Addison's disease) and secondary AI (diseases limiting pituitary ACTH synthesis and secretion). Whilst many of these underlying conditions are believed to be irreversible, for example, the impact of pituitary radiotherapy, there are many situations in which recovery of hypothalamo-pituitary-adrenal (HPA) axis function may occur. As a specific example, the widespread use of glucocorticoid therapy (5, 6), largely for their anti-inflammatory actions, is associated with many adverse effects, including AI as a result of ACTH suppression (7, 8). Indeed, this is probably the commonest form of AI, although almost certainly under-recognized (1).

There are very few studies in the published literature that have approached the assessment of recovery of HPA axis function in a systematic manner (38, 39). In the context of suppressive doses of glucocorticoids, the published studies have examined very small numbers of patients, often in pediatric populations (14, 40). As a result, there has been little consensus as to the components of glucocorticoid exposure (functions of both dose and time) that may contribute to HPA axis suppression and potential recovery (39). Clinicians are therefore often faced with the significant challenge of trying to predict when, and indeed if, HPA axis function will recover. There are currently no published data with which to guide clinicians as to an appropriate frequency of repeat dynamic testing, or information for both the clinician and patient as to the eventual likelihood of restoration of normal adrenal function.

The short *Synacthen* (Corticotropin) test (SST) at the conventional dose of 250µg has been validated against the "gold standard" insulin tolerance test (ITT) to be a reliable tool in the investigation of patients with suspected AI (9-12). In contrast to the ITT, it is a simple test to perform, is well tolerated with very few adverse effects, and is relatively low cost. We, and

others have described the utility of a morning cortisol level to predict SST outcome as a strategy to rationalize the use of dynamic testing (13, 14); however, the results from the SST have the potential to be far more informative. It is well established that the 30-minute cortisol level is used as the criterion to define adequate or inadequate adrenal cortisol reserve, and is the standard by which decisions are made to instigate (or terminate) glucocorticoid replacement. This result provides a read-out as to how the adrenal gland is functioning on that day and whether this is adequate or not. The test results are reliant upon the ability of the adrenal gland to respond to a pharmacological stimulus of synthetic ACTH, and whilst this may be reflected by the 30-minute cortisol, we speculate that the incremental response (delta cortisol: 30-minute - 0-minute) might provide a predictive indicator for future adrenal gland recovery of function.

We have therefore undertaken a retrospective analysis of repeat SSTs performed in patients with potentially reversible causes of AI in order to determine if there are features of the SST results (basal, 30-minute or delta cortisol) that might both guide a strategy for repeat testing and in addition help to identify groups of patients in whom HPA axis function is likely (or unlikely) to be restored.

Materials and Methods

Patient selection

We undertook an observational, retrospective analysis of repeat SSTs performed in three secondary/tertiary care centers across all medical specialties between January 2008 and May 2017 (Oxford University Hospital NHS Foundation Trust, UK; University Hospitals Birmingham NHS Foundation Trust, UK; and Sapienza University of Rome, Italy). During this time, 3942 SSTs were performed in 2535 individuals. Within this cohort, 776 patients were identified as having underlying conditions that could have the possibility of HPA axis function recovery and had undergone at least two SSTs. A total of 1912 SSTs were performed (mean number of tests per patient 2.5 ± 0.8). The mean total duration of follow-up (from first to last SST) was 1182 ± 284 days and the mean time between the first and second SST was 340 ± 322 days. Patient demographics and indications for the SST are presented in Table 1. A subgroup analysis was performed in a cohort of 110 patients either currently taking or having previously been exposed to suppressive doses of glucocorticoid therapy who underwent a total of 277 SSTs. Patients who failed the SST and no longer required glucocorticoid treatment for their underlying medical condition were commenced on hydrocortisone replacement. Inhaled glucocorticoid therapy was continued between SSTs. Tests performed in patients treated with radiotherapy, Addison's disease, congenital adrenal hyperplasia, adrenal metastases, bilateral adrenalectomy or those in whom the indication for the SST was not clearly identified were excluded from the analysis as the potential for restoration of HPA axis function was thought to be limited or could not be determined. All data were collected from electronic medical records.

Cortisol assays

Two cortisol assays were used to analyze samples across the SST; *Siemens ADVIA Centaur* (Siemens Healthcare Diagnostics, Frimley, UK) and the *Roche Modular System* (Roche, Mannheim, Germany). Of the 1912 SSTs that were included in the analysis, 1368 (from 559 patients) were analyzed on the *Roche* assay and 544 (from 217 patients) on the *Centaur*

assay. The same assay was used for repeated testing on the same patient. Serum cortisol analyzed by *Advia Centaur* showed an inter-assay imprecision of 10.5% at 83nmol/L, 6.0% at 524nmol/L, and 7.0% at 904nmol/L and by the *Roche Modular System* of <8% for levels between 76 and 925nmol/L. An analysis directly comparing the results from the Roche and Centaur assays is presented within the Results section.

SST protocol and interpretation

All SSTs were performed between 9 and 12 am, at least 18-hours after the most recent dose of glucocorticoids. Individual clinicians determined the frequency of repeat testing on a case-by-case basis. Patients on the oral contraceptive pill or other estrogen replacement were required to stop the treatment at least 6-weeks before the test. Blood was sampled for serum cortisol at baseline and after 30 minutes: baseline serum cortisol levels were measured prior to injection of 250µg *Synacthen* (Questcor Operations Limited, Dublin, Ireland, for Centaur assays; Alliance Pharmaceuticals, Chippenham, UK - Sigma-tau Pharmaceutical, Rome, Italy, for Roche assays) intramuscularly or intravenously. The 30-minute response to intramuscular or intravenous *Synacthen* has been shown to be equivalent (15). After administration of *Synacthen*, the patients were observed for 15 minutes for signs of any allergic reaction. The interpretation of the SST is based on the 30-minutes serum cortisol where an adequate response to *Synacthen* was defined as >450nmol/L for *Advia Centaur* (16) as >550nmol/L for the *Roche generation I Modular System* (tests done before February 2016)(16), as >450nmol/L for the *Roche generation II* (tests done after February 2016). The incremental response to *Synacthen* was calculated as delta cortisol = [30-minute – 0-minute cortisol].

Statistical Methods

A binomial logistic regression was performed on the whole cohort to ascertain the effects of selected variables on the likelihood that participants will show recovery at the subsequent test. Six variables were inserted into the model: age, sex, 30-minute cortisol, basal cortisol of

the subsequent test, use of steroid medication and different assay used. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed *via* the Box-Tidwell (1962) procedure. A Bonferroni correction was applied using all six terms in the model resulting in statistical significance being accepted when $p < 0.008$. Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable. Data are expressed as median with 95% CI assuming a normal distribution.

Receiver-operating characteristic (ROC) curve analysis was performed using a uniform threshold for any selected variables (basal cortisol (0-minute), delta cortisol, 30-minute cortisol, basal cortisol of the subsequent test) according to the 95% specificity on the ROC analysis. According to this, a cut-off of 100nmol/L (3.6 μ g/dL), 350nmol/L (12.7 μ g/dL), 100nmol/L (3.6 μ g/dL) and 200nmol/L (7.3 μ g/dL) were identified and selected respectively for basal cortisol (0-minute), 30-minute cortisol, delta cortisol and for the basal cortisol of the subsequent test. Area under the curve (AUC) analysis was used to express the overall diagnostic accuracy of the index criterion. Kaplan-Meier survival analysis was conducted to assess the median time to recovery for each group and pairwise log rank comparisons were conducted to determine which group had significant different survival distributions. A $p < 0.05$ was considered indicative of a statistically significant difference. Statistical analyses were performed using SPSS (version 24, Chicago, IL, USA) and GraphPad Prism 7.0 software package (GraphPad Software, Inc. La Jolla, CA, USA).

Results

The patients' characteristics are presented in *Table 1* including the relevant clinical indications as well as the number and timing of the SSTs performed. A total of 776 subjects were recruited, all with potentially reversible causes of AI. A subgroup analysis was performed in 110 patients with AI secondary to treatment with suppressive doses of glucocorticoids.

Overall, 37% of patients of the whole cohort who initially failed the SST eventually went on to pass. 57% of those with non-functioning pituitary tumors and 44% of those patients who underwent pituitary surgery eventually passed the SST.

Logistic regression modeling

The binomial logistic regression model was statistically significant ($\chi^2 = 143.8$, $p < 0.0001$) and explained 47.9% of the variance in adrenal recovery, correctly classifying 88.6% of cases. Sensitivity was 72%, specificity was 94.7%, positive predictive value was 83.2% and negative predictive value was 90.0%. Of the five predictor variables incorporated into the model, two were statistically significant: 30-minute cortisol ($p < 0.0001$) and the basal cortisol of the subsequent test ($p < 0.0001$). Lower 30-minute cortisol and basal cortisol of the subsequent test were associated with an increased likelihood of failing the subsequent test.

HPA axis recovery

All information derived from the SST was examined for its ability to predict whether the subsequent SST would be passed or failed (*Figure 1a, b, c and d*). A 30-minute cortisol $> 350 \text{ nmol/L}$ ($12.7 \mu\text{g/dL}$) was the best indicator for future adrenal recovery (ROC AUC=0.85, *Figure 1e*). In this group, the estimated median time to HPA axis recovery was 334 (95%CI 300-368) days compared with 1368 days (1067 -1668) in those with a 30-minute cortisol $< 350 \text{ nmol/L}$ ($12.7 \mu\text{g/dL}$) ($\chi^2 = 51.2$, $p < 0.0001$). There was a clear stratification of response and those individuals with a 30-minute cortisol between 150 and 350 nmol/L (5.4 and

12.7µg/dL) had a lower chance of recovery of HPA axis function, although recovery was worst in those with a 30-minute cortisol <150nmol/L (5.4µg/dL) (median time to recovery: <150nmol/L =1174 (979-1369) days, $\chi^2= 40.42$, $p<0.0001$; 150-350nmol/L= 465 (288-641) days, $\chi^2= 14.50$, $p<0.0001$) (*Figure 1d*). Combining a 30-minute cortisol level with a delta cortisol of above or below 100nmol/L (3.6µg/dL) did not improve the diagnostic accuracy of the test (ROC AUC=0.84) (*Figure 1f*). The percentages of patients that recovered HPA axis function at 1, 2 and 4 years after their initial SST are presented in supplementary table 1.

In order to improve further the accuracy of the test, we combined the use of the 30-minute cortisol with the baseline cortisol of the subsequent SST, which was assumed to reflect a 'random morning cortisol' (assessed between 9 and 12 am) in the absence of replacement therapy (>18hours). The mean time between the first SST and random cortisol was 340 ± 322 days. In the group with a 30-minute cortisol <350nmol/L (12.7µg/dL) and a subsequent random morning cortisol <200nmol/L (7.3µg/dL), 93% of individuals continued to have AI at 4-years (median time to recovery 2083 (1928-2238) days, $\chi^2= 17.48$, $p=3\times10^{-5}$; ROC AUC=0.95) (*Figure 1g*). The proportion of patients recovering HPA axis over time in the whole cohort are presented in *Figure 2*.

The results of the analysis were not altered when corrected for both age and gender. In addition, a further analysis was undertaken in which only patients that failed their first test were included (n=248), and the results were not different from those presented above (*Supplementary Figures 1 and 2*).

HPA axis recovery in glucocorticoid-exposed patients

In the majority of cases, patients treated with suppressive doses of glucocorticoids do not have underlying endocrine disease and therefore a dedicated subgroup analysis on these patients was performed (n=110). In this group, the delta cortisol was the best predictor for future adrenal recovery: those patients with a delta cortisol >100nmol/L (3.6µg/dL) had a

shorter estimated median time to recovery (262 (212-312) vs. 974 (633-1314) days, $\chi^2=20.233$, $p=7.0 \times 10^{-6}$; ROC AUC= 0.77) (*Figure 3a,b, c and d*).

Combining the delta cortisol <100nmol/L (3.6 μ g/dL) with the subsequent random cortisol (above or below 200nmol/L) helped to refine the predictive ability of the test; patients who had a random morning cortisol >200nmol/L (>18h after their last replacement dose) following their initial SST had a median time to HPA axis recovery of 322 (134-357) days. No patient who had a subsequent random cortisol <200nmol/L recovered from their iatrogenic adrenal insufficiency over the 4-year duration of the study. The results of the analysis were not altered when delta cortisol values were corrected for baseline (0-minute) cortisol levels (data not shown). The proportion of glucocorticoid-exposed patients recovering HPA axis over time are presented in *Figure 4*.

Comparison between cortisol assays

As described above, two different cortisol assays were used in this cohort study. In the main cohort, the logistic regression model as well as the ROC analysis did not show significant differences between assays. However, to confirm these findings, an analysis was performed for each assay individually using the value of the 30-minute cortisol and the subsequent random morning cortisol. Surprisingly, a 30-minute cortisol of 350nmol/L (12.7 μ g/dL) and a random morning cortisol of 200nmol/L (7.3 μ g/dL) represented the 95% specificity in the ROC analysis for both the assays. In addition, the proportion of patients that subsequently went on to pass the SST at 1, 2 and 4 years was entirely comparable between assays (1 year: 55 vs. 57%; year 2: 88 vs. 89%; year 4: 98 vs. 99%. *Roche vs. Centaur*, supplementary table 2).

Discussion

We have demonstrated that the stimulated 30-minute cortisol from the short *Synacthen* can be used to predict the likelihood of HPA axis recovery. Furthermore, combining these measurements with assessment of a 1-year random morning cortisol measurement (between 9 and 12 am and >18 hours after the last replacement dose) provides an accurate prediction of those individuals who are likely to recover adrenal function and those in whom it may not. Notably, 57% of our patients with non-functioning pituitary tumours and 44% of those patients who underwent pituitary surgery recovered HPA axis function at subsequent testing. This implies that there is significant potential for reversibility of secondary AI in these patients. We (13) and others (39) have previously described the use of a morning cortisol to assess adrenal reserve, but to date, there has been very little attempt to use the SST to inform a strategy for repeating testing that in addition might serve as a guide as to the likelihood of restoration of HPA axis function.

There is currently a lack of consensus as to how and when to assess patients with pituitary disease for recovery of HPA axis function after surgery. Different approaches have been proposed including the use of a baseline morning cortisol (12, 13, 17, 18), SST (19), or the 'gold standard' ITT (20, 21). The timing of post-operative testing is also not uniform with significant variability across centers (24h, 48h, 1-6 weeks) (17). Further testing beyond this time point (6-weeks) is not regarded as routine and performed in some centers, but not in others. If a patient fails a SST post-operatively, they may end up on life-long glucocorticoid replacement therapy. However, cases where recovery of HPA axis function is delayed are reported (20). More recently, a study has suggested that a significant number of patients with underlying pituitary tumors, including those that have had surgery, may recover over a median duration of 20 months (range 8-51) (18).

Taken together with our data, this would suggest that repeat assessments of the HPA axis are clearly justified. We have therefore proposed that in those individuals in whom there is the potential to recover from AI, the strategy for repeat testing could be guided by their SST results. In our cohort, those individuals who had a 30-minute cortisol level >350nmol/L

(12.7µg/dL) were likely to recover more quickly and therefore 6-monthly testing could be advocated. In contrast, the rate of recovery in those with a 30-minute cortisol <350nmol/L (12.7µg/dL) was much slower and annual testing may be more appropriate in this group. Furthermore, we found that the use of a random morning cortisol could help to identify the group of patients who were most likely to recover HPA axis function and allow further rationalization of dynamic testing (*Figure 5*).

The increasing use of glucocorticoid therapy has led to a dramatic increase in the awareness and diagnoses of secondary adrenal insufficiency in the context of 'iatrogenic Cushing's syndrome'. It is estimated that 2-3% of the population of the UK and USA are taking prescribed glucocorticoids, and these are most commonly used in the more elderly populations and at doses that are known to suppress the HPA axis (22). Data on recovery of the HPA axis after exposure to suppressive dose of glucocorticoids are limited and often in studies that have recruited small numbers of patients (ranging from n=1 to 49) (23-32, 39). In addition, much of the published literature has been in pediatric populations (33-37) and therefore simple extrapolation into the adult setting is not straightforward. These studies are limited not only in the variability of the populations that they have studied, but also in the differences in duration and dose exposure to glucocorticoids. As a result, the published literature that is currently available does not allow us to determine whether the duration, dose or cumulative glucocorticoid exposure are the main drivers to the development of secondary AI in this context (38). There is significant variability between individuals in their susceptibility to the development of the adverse metabolic effects associated with glucocorticoid use, and it is highly likely that the same will apply to the development (and subsequent potential for recovery) of HPA axis suppression.

In total, 43% of our patients who at the time of their SST were either currently, or previously exposed to suppressive doses of glucocorticoids, regained HPA axis function. Based upon the results of the initial SST undertaken at steroid withdrawal, in this subgroup of patients, the delta cortisol was the best predictor of future recovery of HPA axis function, such that

95% of patients who had an initial delta cortisol $>100\text{nmol/L}$ ($3.6\mu\text{g/dL}$) passed the SST within 4 years. Whilst 4-year recovery rates were lower in the delta cortisol $<100\text{nmol/L}$ (67%), combining this with a subsequent random morning cortisol identified a group of patients who were unlikely to recover from the AI (0% recover at 4-years for those with a subsequent random cortisol $<200\text{nmol/L}$, $7.3\mu\text{g/dL}$). However, we acknowledge that this analysis was only undertaken in a small sub-cohort ($n=32$) (Figure 4), and requires confirmation in larger studies. As with the whole cohort discussed above, this stratification could be used to guide the frequency of repeat testing, and an algorithm is presented in Figure 5. Our analysis did not show differences in recovery rates between patients taking different steroid formulations. The majority of our patients had been taking prednisolone (49.5%), but the small numbers of individuals taking other preparations, as well as limitations in the availability of data relating to the exact dose and timing do not allow us to make detailed comments or analysis with regards to the precise nature of the glucocorticoid exposure that might dictate the SST response. An additional limitation is the continuation of exposure to suppressive doses of glucocorticoid therapy between SSTs which is likely to have occurred in the majority of patients taking inhaled steroid treatment.

Surprisingly, even though we have used assay-specific thresholds for defining a pass or fail of the SST, the logistic regression model demonstrated the independence of the analysis from the different assay methods used. The results for each assay (assessed independently) suggesting that the same threshold of a 30-minute cortisol of $>350\text{nmol/L}$ and a 1-year random morning cortisol of $>200\text{nmol/L}$ (after 18 hours of steroid withdrawal) can be used. The reasons underpinning this are not entirely clear, although clearly results of the SST in this analysis are being used in a different context in this analysis (i.e. predicting recovery in future tests as opposed to assessing current HPA axis integrity). Further analysis across larger cohorts and including additional assays is clearly warranted.

Importantly, in our study there are significant limitations. This is a retrospective analysis of clinical data obtained from electronic patient records and therefore there is the potential for selection bias in those individuals undergoing short *Synacthen* testing. We do not have

accurate data on the dose and duration of exposure to glucocorticoids, and therefore we are unable to answer questions that relate to cumulative exposure that might predict AI. However, this does represent the largest analysis of this kind published to date. Our data extend to approximately 4-years of follow-up and therefore it is not possible to say whether further recovery of the HPA axis may occur after this time point. The algorithm that we have proposed is designed to guide and help the clinician, but is only derived from this data-set and have not been tested or validated in other cohorts. As a result, it is important that individual clinicians use their discretion and clinical judgment in the frequency and interpretation of dynamic assessments of HPA axis function.

In conclusion, the results generated from the 250µg SST can provide useful information for both the clinician and patient to guide the frequency of repeat testing as well as the likelihood of HPA axis recovery. When combined with a subsequent random morning cortisol, the diagnostic accuracy improves significantly. Finally, this analysis has the potential to rationalize the use of the SST; with the cut-offs proposed in the algorithm (*Figure 5*), 27% of SSTs could have been avoided, limiting both inconvenience for the patient and reducing medical and nursing costs.

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495 **Table 1:** Baseline characteristics of 776 patients with reversible causes of adrenal insufficiency.
 496 Patients treated with radiotherapy, or who had been diagnosed with Addison's disease, congenital
 497 adrenal hyperplasia, adrenal metastases or who had undergone bilateral adrenalectomy were
 498 excluded from the study. Data are expressed as mean±standard deviation where appropriate.
 499 Figures in parentheses reflect % of the entire cohort. (SST: short *Synacthen* (corticotropin) test).
 500

	Whole cohort	Glucocorticoid exposed
n	776	110
Age (years)	53±18	53±17
Total number of SSTs	1912	277
Number of SSTs per patient	2.5±0.8	2.5±0.9
Total duration of follow-up (days)	1182±284	1166±466
Time between first and second SST (days)	340±322	268±215
Sex		
Male	335 (43%)	50
Female	441 (57%)	60
SST Indication		
Previous treatment with suppressive doses of glucocorticoids (<i>topical, nasal, inhaled, oral, intramuscular, intravenous</i>)		110 (14%)
<i>Prednisolone</i>		49
<i>Hydrocortisone</i>		18
<i>Dexamethasone</i>		3
<i>Others (budesonide, fluticasone, ciclesonide, beclometasone)</i>		40
Post-operative following pituitary surgery	120 (15%)	
Pituitary adenoma (<i>Non-functioning, no surgery, no radiotherapy</i>)	136 (17%)	
Others central nervous system tumors	154 (20%)	
Other pituitary conditions (<i>including hypophysitis</i>)	42 (5%)	
Adrenal disease (<i>including unilateral adrenalectomy, adenoma, carcinoma</i>)	34 (4%)	
Other indications (<i>autoimmune disease, hyponatremia, vomiting, weight loss, hyperkalemia, hypoglycemia, hypotension, collapse, fatigue</i>)	180 (23%)	

Figure Legends

Figure 1

Kaplan-Meier plots estimating time to recovery of HPA axis function in 776 patients with potentially reversible causes of adrenal insufficiency stratified by basal (0-minute) cortisol of the same test (a), delta cortisol (30-minute – basal cortisol) (b), 30-minute cortisol (c), 30-minute cortisol stratified by cut-offs at >350, 150-350, <150nmol/L (d) using data from their initial SST. ROC curve analysis to determine the ability of the characteristics of the initial SST to predict eventual recovery of adrenal function (e). Combining 30-minute cortisol with delta cortisol (30-minute – basal cortisol) levels does not improve the ability to predict passing a subsequent SST (f). In those patients with a 30-minute cortisol <350nmol on their initial SST, a subsequent random morning cortisol (>18hours after the last replacement dose) of >200nmol/L significantly increases the likelihood of HPA axis recovery (g) (SST: short *Synacthen* (corticotropin) test; ROC: receiving operating curve; AUC: area under the curve).

Figure 2

HPA axis recovery rates after short *Synacthen* (corticotropin) testing in 776 patients with potentially reversible causes of adrenal insufficiency, including non-functioning pituitary tumors and pituitary surgery.

Figure 3

Kaplan-Meier plots estimating time to recovery of HPA axis function in 110 patients with adrenal insufficiency due to exposure to suppressive doses of glucocorticoid therapy, stratified by basal (0-minute) cortisol of the same test (a), 30-minute cortisol (b) and delta cortisol (30-minute – basal cortisol) (c), of their initial SST. ROC curve analysis to determine the ability of the characteristics of the initial SST to predict eventual recovery of adrenal

function (d). (SST: short *Synacthen* (corticotropin) test; ROC: receiving operating curve;
AUC: area under the curve).

Figure 4

HPA axis recovery rates after short *Synacthen* (corticotropin) testing in 110 patients
previously exposed to suppressive doses of glucocorticoid therapy.

Figure 5

Proposed flow-chart for the use of short *Synacthen* (corticotropin) testing in patients with
potentially reversible causes of adrenal insufficiency. (* Random morning cortisol was
measured between 9 and 12 am and at least 18h after the last dose of glucocorticoid).