Tests of adrenal insufficiency

J C Agwu, H Spoudeas, P C Hindmarsh, P J Pringle, C G D Brook

Abstract

Aim—In suspected adrenal insufficiency, the ideal test for assessing the hypothalamo–pituitary–adrenal axis is controversial. Therefore, three tests were compared in patients presenting with symptoms suggestive of adrenal insufficiency.

Method—Responses to the standard short Synacthen test (SSST), the low dose Synacthen test (LDST), and the 08:00 hour serum cortisol concentration were measured in 32 patients. A normal response to the synacthen test was defined as a peak serum cortisol of ≥ 500 nmol/l and/or incremental concentration of ≥ 200 nmol/l. The sensitivity and specificity of the 08:00 hour serum cortisol concentration compared with other tests was calculated.

Results—Three patients had neither an adequate peak nor increment after the SSST and LDST. All had a serum 08:00 hour cortisol concentration of < 200 nmol/l. Eight patients had abnormal responses by both criteria to the LDST but had normal responses to the SSST. Three reported amelioration of their symptoms on hydrocortisone replacement. Twenty one patients had a normal response to both tests (of these, 14 achieved adequate peak and increment after both tests and seven did not have an adequate peak after the LDST but had a normal increment). The lowest 08:00 hour serum cortisol concentration above which patients achieved normal responses to both the LDST and SSST was 500 nmol/l. At this cut off value (compared with the LDST), the serum 08:00 hour cortisol concentration had a sensitivity of 100% but specificity was only 33%.

Conclusion—The LDST revealed mild degrees of adrenal insufficiency not detected by the SSST. The value of a single 08:00 hour serum cortisol concentration is limited.

Keywords: Synacthen; adrenal insufficiency; hypothalamo–pituitary–adrenal axis

Plasma cortisol secretion follows a circadian pattern with the highest concentrations being seen in the morning. A single estimation of the 08:00 hour serum cortisol concentration reflects endogenous activity of the hypothalamo–pituitary–adrenal axis.1 However, it is uncertain what cut off values should be used.5,6 The cortisol response to insulin induced hypoglycaemia has been validated against the response to surgical stress and is one of the most valuable tests of adrenal insufficiency. Unfortunately, it is both unpleasant and potentially dangerous7 and there remains a need for a simple, safe, and reliable screening test.

The standard short Synacthen test (SSST), in which a pharmacological dose of adrenocorticotrophic hormone (ACTH; 250 µg/1.73 m²) is given intravenously, directly measures adrenal reserve. It is also thought to assess hypothalamo–pituitary function indirectly, because chronic ACTH deficiency leads to a quiescent adrenal gland and therefore to an inadequate cortisol response to exogenous ACTH. The peak serum cortisol concentration obtained 30 minutes after the SSST has been shown to correlate with that obtained after insulin induced hypoglycaemia.7,8 Some patients with normal responses to the SSST have been shown later to have adrenal insufficiency.9–10 The lowest dose of ACTH capable of eliciting a maximum response of cortisol in healthy children and adults is 500 ng/1.73 m².9–12 This dose of ACTH, which is 500 times less than that used in the standard test, leads to a rise in serum cortisol concentration over the first 20 minutes identical to that obtained after injection of the standard dose12–14 and is the dose used in the low dose synacthen test (LDST). The LDST may provide a more sensitive test of adrenal function.

We assessed the 08:00 hour serum cortisol concentration and responses to the LDST and SSST in 32 patients presenting with symptoms suggestive of adrenal insufficiency.

Patients and methods

Thirty two patients (18 girls and 14 boys) aged 2–19 years presented with symptoms suggestive of adrenal insufficiency. Fourteen had been irradiated for brain tumours (six medulloblastomas, three astrocytomas, one optic glioma, one pituitary germ cell, one pineal tumour, one neuro-ectodermal tumour, and one basal ganglia tumour); two had total body irradiation for relapsed non-Hodgkin’s lymphoma and acute lymphoblastic leukaemia; 13 had other endocrinopathies (four isolated growth hormone deficiencies, three
panhypopituitarism, one precocious puberty, one transphenoidal surgery for pituitary gigantism, one congenital adrenal hyperplasia, one delayed puberty, one autoimmune thyroiditis, one hypocalcaemia; two had growth hormone deficiency; and one had histiocytosis with prolonged dexamethasone treatment.

The study was approved by the local ethics committee.

HORMONE ASSAY

Cortisol was measured using a direct coated tube assay (Euro DPC Ltd, Llanberis, Gwynedd, UK). This assay has a lower limit of detection of 6 nmol/l. The within assay coefficients of variation were 5.7% and 2.6% at serum concentrations of 28 nmol/l and 552 nmol/l, respectively. The between assay coefficients of variation were 9.1% and 6.8% at serum concentrations of 95 nmol/l and 459 nmol/l, respectively.

STATISTICAL ANALYSIS

A normal cortisol response was defined as a peak of \( \geq 500 \text{ nmol/l} \) and/or an increment from the basal concentration of \( \geq 200 \text{ nmol/l}. \)

The peak and increment following the SSST were plotted against results obtained after the LDST. The sensitivity and specificity of the 08:00 hour serum cortisol concentration compared with the other tests was calculated using standard techniques.

Results

The relation between the peak serum cortisol concentration obtained after the SSST and LDST is shown in fig 1A. Figure 1B compares the increment from basal values between these two tests. Three patients achieved neither an adequate peak nor increment to either the SSST or LDST. All had a serum 08:00 hour cortisol concentration of \(< 200 \text{ nmol/l} \). Eight patients had abnormal responses on both criteria to the LDST but had normal responses after the SSST. Three who were offered hydrocortisone replacement treatment have reported amelioration of their symptoms. Twenty one patients had normal responses to both tests. Of these, 14 had an adequate peak and increment after both tests, whereas seven had an inadequate peak only after the LDST but had a normal increment after both tests. These results are summarised in table 1.
Discussion

Broadly, there are two groups of patients in which it is necessary to assess adrenal function. The first group comprises those presenting with suggestive symptoms (lethargy, weight loss, anorexia, nausea, vomiting, hyperpigmentation, shock, hypoglycaemia, and electrolyte imbalance). The other group comprises those at risk of developing adrenal insufficiency. This includes patients who have had previous glucocorticoid treatment at supraphysiological doses, cranial irradiation, hypothalamic–pituitary disease, or pituitary surgery. Although the diagnoses of our cohort are varied, they all presented with symptoms that made adrenal insufficiency part of the differential diagnosis. Twenty-one of our patients with suggestive symptoms had normal results to both SSST and LDST, showing how non-specific most of the symptoms are.

The ideal test for diagnosing hypothalamic–pituitary–adrenal insufficiency needs to be easy to perform, safe, and reliable. The SSST is widely used as a screening test. However, in patients with recent onset hypopituitarism, there is a risk of obtaining false normal results using the SSST because in such patients the adrenal gland will retain its ability to respond to ACTH. Recently, Soule et al reported failure of the SSST to diagnose unequivocally a 51 year old woman with long standing symptomatic secondary hypoadrenalism.19 Graybeal and Fang showed that by the direct measurement of ACTH concentrations, the dose of ACTH used in the SSST far exceeded that produced physiologically in response to insulin induced hypoglycaemia,20 which may account for the misleading results that are obtained occasionally. In our patients, the SSST showed a positive bias when compared with the LDST. It has been suggested that increasing the cut off value of peak serum cortisol obtained after the SSST to 600 nmol/l might improve sensitivity,19 but this was not the case in our cohort. The dose of ACTH used in the LDST is 500 times smaller than the standard dose and reflects peak endogenous secretion. Jones et al found that, at a cut off value of 500 nmol/l, early morning cortisol concentration had a sensitivity of 100% when compared with the cortisol response to insulin induced hypoglycaemia.7 This agrees with our results. However, the specificity at this cut off value was poor. Other authors have shown that an early morning cortisol concentration of < 100 nmol/l is indicative of adrenal insufficiency.2 In our study, all patients who failed the LDST had 08:00 hour serum cortisol concentrations of < 200 nmol/l. Patients who have early morning serum cortisol concentrations between 100 nmol/l and 500 nmol/l need to be investigated using other tests to ascertain their adrenal function status.

Although the timing of peak cortisol measurements after the LDST was variable in our patients, the same conclusion would have been drawn if the sampling time had been limited to 0, 10, 20, or 30 minutes.

The LDST is performed in the afternoon when basal cortisol concentrations are low, and this test can be performed as an outpatient procedure.

The LDST detected patients with adrenal insufficiency who had normal responses to SSST and we recommend that it should replace the SSST as the initial screening test in patients in whom adrenal insufficiency is suspected. In patients with borderline results to LDST it may be prudent to perform an insulin tolerance test.


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