The Short Synacthen Test may be more sensitive than the Glucagon Stimulation Test in assessing the Hypothalamic Pituitary Adrenal Axis: A retrospective audit

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Introduction

Evaluation of the Hypothalamic-Pituitary-Adrenal axis (HPA) can be challenging. Concern regarding test reliability and variability in interpretation of investigations due to gender, age and lack of standard assays is well reported.[1,2]

Insulin-induced hypoglycaemia with the Insulin Tolerance Test (ITT) is considered the gold standard assessment of HPA integrity.[3] The Short Synacthen Test (SST) is a relatively simple, low-cost and well tolerated first line test of HPA despite concerns regarding accuracy.[4] The glucagon stimulation test (GST) is often used as an alternative to the ITT. Although less reliable, the GST is particularly useful when induced hypoglycaemia is contra-indicated.[5]

Misdiagnosis of HPA integrity can lead to a lifetime of unnecessary steroid treatment or under-replacement with subsequent ill health and life threatening emergencies; therefore accurate investigation of the HPA is essential. In this audit we evaluated the sensitivity of SST and GST in comparison to ITT for the assessment of patients with clinically suspected HPA insufficiency.

Objectives

We retrospectively audited test results of all patients referred to our unit for the assessment of HPA during a two year period from 2007 to 2009. The audit objectives were:

- To analyse local indications for HPA assessments.
- To evaluate accuracy of the SST and GST against the ITT with the aim of advising the best method to screen for HPA insufficiency.

Method

During the two year audit period we identified 32 patients who underwent ITT for assessment of HPA, of whom 31 had pre-screening SST and/or GST and were included in the analysis.

Case notes and laboratory results of the 31 patients were reviewed for the indication of HPA assessment and to ensure all three dynamic tests were performed according to the unit protocol.

Appropriate cortisol response was considered as a peak value of ≥500 nmol/L on ITT and GST, and 30 minute value ≥550 nmol/L on standard SST (580 nmol/L in women taking oestrogens/OCP).

Serum cortisol was determined by chemiluminescent microparticles immunoassay (CMIA) using Abbott Architect (Ref 8D15, JL840685/R06), Abbott Laboratories, Abbott Park, IL 60064 USA with run precision of approx. CV 4% and total approx. CV 5% and lower limit of detection 22 nmol/L.

Analysis of data was provided by an independent statistician to generate sensitivity and specificity via cross-tabulation.

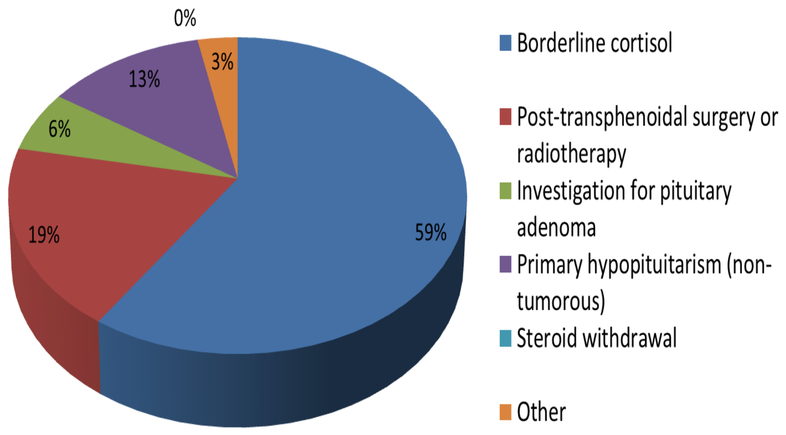
Results

Sample (n) = 31

21 were females

Average age was 42.9 years (range 19 - 64)

Fig 1. Indication for ITT



Indications for ITT (Figure 1):

- 23 with clinically suspected hypopituitarism.
- 6 post-transphenoidal surgery.
- 2 with none ACTH-producing pituitary adenoma

SST Versus ITT (Table 1):

26 of the 31 patients underwent both SST and ITT. 13 patients failed both SST and ITT. Only one patient passed SST but failed ITT, giving an SST sensitivity of 92.8% (CI 86.1% – 99%).

11 patients passed ITT. All but one failed the SST, giving SST a specificity of 8.3% (CI 4%- 16.2%).

Table 1: Cross tabulation comparing SST and ITT

		ITT Max cortisol >500		Total
		0 (Failed)	1(Passed)	
SST 30min cortisol >550	0 (Failed)	13	11	24
	1 (Passed)	1	1	2
Total		14	12	26

GST Versus ITT (Table 2):

16 of the 31 patients underwent both GST and ITT

Of these 6 failed both GST and ITT, however 2 passed GST but failed the ITT giving GST a sensitivity of 75% (CI 75% - 94.7%)

None of the 8 patients who passed the ITT have passed the GST giving a specificity of 0% (CI 0% - 19.7%)

Table 2: Cross tabulation comparing ITT and GST

		ITT Max cortisol >500		Total
		0 (Failed)	1(passed)	
GST max cortisol > 500	0 (Failed)	6	8	14
	1(Passed)	2	0	2
Total		8	8	16

Discussion

Reports of increasing latency between first symptoms and diagnosis of adrenal insufficiency is concerning. Delay in diagnosis is associated with significantly lower quality of life which highlights the need for prompt investigations using reliable and accurate biochemical tests.[6]

Our audit sample included patients who were referred with clinical suspicion of hypoadrenalism and hence reflects the actual clinical practice where a combination of HPA investigation and clinical assessment are needed for accurate diagnosis.[7] All patients had at least two dynamic tests including ITT carried according to the usual agreed protocols.

The most common indication for assessment of HPA integrity in our sample was investigation of a borderline cortisol which accounted for 59% of all cases, with post-transphenoidal surgery and primary hypopituitarism making 32% of the rest.

In this audit the 30-minute SST cortisol value was more sensitive in predicting HPA insufficiency when compared to the gold standard ITT than the peak cortisol value obtained during GST, with respective sensitivity of 92.8% (CI 86.1% – 99%) for SST and 75% (CI 75%- 94.7%) for GST. This result is in line with the finding by Berg et al who compared GST against ITT in adult patients post pituitary surgery and concluded that 51% of the sample tested for HPA integrity would have not been diagnosed with accuracy if GST was used as the sole test. GST sensitivity on this study ranged from 32% to 72%.[8]

Both SST and GST in our sample had a low specificity when compared to ITT with values of 8% and 0% respectively. Attempts on improving specificity by increasing the cut off limit for either test would have led to compromise on sensitivity; a factor which could hinder the validity and utility of these tests as a screening tool for HPA insufficiency.

The limitation of this audit is the small sample, however, we feel it represents a true case mix encountered in the usual clinical practice and reflect the day to day performance of the two common screening tests.

Conclusion

Review of results from this retrospective audit suggest that the standard Short Synacthen Test is a more sensitive screening tool than the Glucagon Stimulation Test in assessing the integrity of the Hypothalamic Pituitary Axis.

Recommendation

SST is a more appropriate screening test for HPA axis and should replace the GST when ITT is contraindicated.

Confirmation of these results in a larger cohort is warranted.

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