

Outpatient synacthen testing in a large metropolitan region: a clinical audit

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ABSTRACT

AIM: To audit short synacthen tests (SSTs) performed at a single laboratory within the greater Auckland area.

METHODS: Two hundred and eighty-seven SSTs conducted in 286 individuals between September 2016 and September 2019 were assessed. Test requests were not triaged. We assessed source of referrals, indications for testing, adequacy of pre-test information and test outcomes.

RESULTS: Seventy-one percent of referrals were for women. Fifty-six percent were from primary care and 18% from rheumatology. One-hundred and fifteen (40%) of those referred had been taking corticosteroids within the previous three months: this information was only provided in 49 referrals. In 32% of referrals, no serum cortisol measurement had been undertaken within the previous six months. In 20% of referrals, no indication was provided. Thirty-three (11%) SSTs were abnormal. Of these, 29 were in patients taking corticosteroids. No SSTs were abnormal among 64 patients with pre-test serum cortisol >300nmol/L or >400nmol/L according to the cortisol assay in use.

CONCLUSIONS: Referrals for SSTs often lack important information, such as the indication for testing and recent corticosteroid exposure. Up to one quarter of SSTs could be avoided if a serum cortisol was routinely measured prior to referral. Adopting a structured referral form that mandates provision of important clinical and biochemical data might reduce unnecessary testing.

Adrenal insufficiency is an uncommon but important clinical syndrome that can be caused by endogenous pituitary or adrenal pathology, or exogenous administration of corticosteroid medications.¹ The short synacthen test (SST) is commonly used for the diagnosis of adrenal insufficiency because of its relative ease and safety compared with the metyrapone stimulation test or the insulin tolerance test.^{2,3} The level of cortisol response to synacthen deemed adequate for exclusion of adrenal insufficiency varies by assay.

A clearly low, early morning plasma cortisol may be predictive of a subnormal SST response, and a clearly robust plasma cortisol may be predictive of a normal SST response.⁴ In these situations the SST may not be necessary. The specific cut-offs for a low or robust cortisol vary by assay and

depend on the desired sensitivity and specificity for prediction of SST outcomes.⁴⁻¹¹

Prudent use of diagnostic tests is important: avoiding unnecessary testing allows better use of limited health resources, reduces waiting times for those with a definite need for the test and avoids the risks of invasive testing. The estimated cost of an SST in our public hospital service, including the cost of the synacthen, the cost of plasma cortisol testing and nursing time and equipment, is NZ\$200.

Since 2016, our service has conducted all outpatient SSTs in the greater Auckland area, which has a population of approximately 1.7 million. We audited the SST requests and results over a three-year period. Our aims were to determine whether the SST was being used appropriately and to

identify areas for improvement, including an estimation of the proportion of potentially avoidable tests.

Methods

Study population

We undertook an audit of outpatient SSTs performed in the greater Auckland area between September 2016 and September 2019. During this time, our department was the sole referral centre for outpatient SSTs. No triaging was applied to the test referrals during this period. We excluded referrals of patients with known or suspected pituitary disease and those from endocrinology specialists.

Referral and demographic data

Referrals were received in either paper or electronic format. Each referral format was configured as free-text only. Data were extracted from the referrals on patient age and gender, referrer specialty, the indication(s) for SST, the timing, dose and route of administration of recent or concomitant corticosteroid therapy, and previous plasma cortisol levels, including the time of collection. To supplement this information, patients were asked on the day of the SST whether they were taking corticosteroid medications and, if so, the dose and route of administration. In addition, we searched the electronic patient record for prescriptions of corticosteroids within three months of the SST, and for serum cortisol measurements obtained within six months of the SST. All cortisol measurements performed within the catchment area are accessible by this means.

Pre-SST and basal plasma cortisol measurements

Measurements of plasma cortisol obtained prior to the SST were performed using either the Siemens assay or the Roche Cortisol II assay. We used data collected by the assay manufacturers to code the results:

- Siemens assay
 - Robust: >400nmol/L
 - Intermediate: 200–400nmol/L collected between 7am–10am, or <200nmol/L collected after 10am
 - Low: <200nmol/L collected between 7am–10am

- Roche Cortisol II assay
 - Robust: >300nmol/L
 - Intermediate: 170–300nmol/L collected between 7am–10am, or <170nmol/L collected after 10am
 - Low: <170nmol/L collected between 7am–10am

If no cortisol measurement had been performed prior to the SST, we considered the zero-minute serum cortisol from the SST as representative of a pre-SST value, and coded it using the same method.

Short synacthen tests

Testing was performed between 7am and 10am where possible. Cortisol samples were drawn from an intravenous cannula immediately prior to, and 30 minutes after, administration of 250µg intravenous synacthen. Patients known to be receiving oral corticosteroid therapy were asked to withhold it for 24 hours prior to testing. Plasma cortisol was measured using the Roche Cortisol II assay (Modular Analytics E170). A 30-minute post-synacthen plasma cortisol >400nmol/L was defined as a normal response. The Roche Cortisol II assay is more specific than previous assays for cortisol due to lower levels of cross reactivity with cortisol metabolites. As a result, reported reference ranges are lower than for the Roche Cortisol I assay.¹²

Analyses

Outcomes of interest included the proportion of SST results that were abnormal (30-minute post-synacthen plasma cortisol <400nmol/L), the prevalence of pre-test cortisol measurements, the prevalence of pre-test corticosteroid treatment and the indications for testing. We assessed the proportion of abnormal SSTs according to pre-test cortisol values and the use of pre-test corticosteroid therapy.

This work is a clinical audit, so ethics review was not required.

Results

Dataset of eligible tests

During the audit period, 353 SSTs were performed in 352 patients. After exclusion of referrals by endocrinologists (n=64) and those with known or suspected pituitary disease (n=11), 287 tests performed in 286

patients were eligible for analysis. Table 1 shows the demographic data for those tested. The majority were women. Forty percent had been prescribed corticosteroid therapy in the three months before SST was performed. No pre-SST plasma cortisol measurement was available for 33%.

Sources of referrals and test outcomes

Table 2 shows the sources of referrals. More than half were from primary care, and nearly 20% from rheumatology. Other specialities each generated fewer than seven referrals per year. The table also shows the wide range of proportions of abnormal tests among referral sources. One in three tests requested by rheumatology was abnormal. No tests requested by cardiology or immunology were abnormal. Other disciplines had similar proportions of abnormal tests, ranging from 6% to 14%.

Indications for SST

Table 3 sets out the indications for the SST provided by the referrers. No indication was provided in 20% of referrals: a similar proportion (17%) of referrals mentioned prolonged corticosteroid therapy as the indication for SST. Of the 105 referrals for the indication “low basal cortisol,” four (4%) did not have a cortisol measured within the previous six months, and 44 (42%) had a robust or intermediate pre-SST cortisol. Indications mentioned in fewer than five referrals were grouped as “other.” These included suspected adrenal tuberculosis, treatment with an immune checkpoint inhibitor, low or high adrenocorticotrophic hormone (ACTH), skin pigmentation, adrenal fatigue, adrenal metastatic disease, radiotherapy involving the adrenal glands, unilateral adrenalectomy, salbutamol use, other autoimmune disease and a family history of Addison’s disease.

Table 1: Characteristics of patients referred for short synacthen tests. Data are mean (range) or N (%).

Characteristic	
Age, y	49 (12-88)
Female	203 (71%)
Corticosteroid prescribed in the previous three months	115 (40%)
No serum cortisol in the previous six months	94 (33%)

Table 2: Referrers and proportions of abnormal tests. Data are N or N (%).

Referring Specialty	N	Abnormal SST
General practice	160	10 (6)
Rheumatology	53	18 (34)
Immunology	19	0 (0)
General internal medicine	14	2 (14)
Cardiology	12	0 (0)
Infectious disease	8	1 (13)
Other*	21	2 (10)
Total	287	33 (12)

*Specialties with <5 referrals each

Corticosteroid use

One hundred and fifteen referrals (40%) were for patients either currently taking corticosteroids or who had been exposed to corticosteroid drugs within the previous three months. Of these, only 49 (43%) mentioned corticosteroid exposure. Information about duration of corticosteroid use, timing of administration during the day and the dose used leading up the SST was rarely available.

Pre-SST serum cortisol measurements

One hundred and ninety-four patients (68%) had a serum cortisol measured within six months of the referral for the SST. This information was contained in only 119 (64%) of these referrals. The numerical value was provided in only 33 (17%).

SST results

Of the 287 SSTs, 33 (11%) were abnormal. Among the 33 abnormal SSTs, 15 (45%) had a basal cortisol <100nmol/L, 12 (36%) had a basal cortisol 100–170nmol/L and six (18%) had a basal cortisol >170nmol/L. Twenty-nine abnormal SSTs occurred in patients receiving corticosteroid therapy. Table 4 shows the number of abnormal SSTs in corticosteroid-treated (N=115) and non-corticosteroid-treated patients (N=172). An abnormal SST occurred in 25% of patients receiving corticosteroid therapy (29/115). This was almost exclusively (26/29, 90%) in patients receiving oral, intramuscular

or intra-articular corticosteroids. Three abnormal SSTs were in patients receiving topical or inhaled corticosteroids, and all these patients were receiving potent topical corticosteroids. Among patients not receiving corticosteroids, 2% (4/172) had an abnormal SST. There were no abnormal SSTs among non-corticosteroid-treated patients who had not had a cortisol measurement prior to the SST (0/47).

None (0/64) of those with a robust basal plasma cortisol had an abnormal SST, irrespective of corticosteroid treatment. Almost half of the patients receiving corticosteroid therapy who had a low basal cortisol (26/55) had abnormal SSTs. A similar proportion of patients with a basal cortisol level <100nmol/L (7/14, 50%) had an abnormal synacthen test. Eleven of these 14 were prescribed corticosteroid in the preceding three months.

Discussion

In this retrospective audit of SSTs, we assessed referrals for, and the results of, SSTs. Several clinically helpful results ensued. All patients with a robust basal cortisol (>300nmol/L for Roche Cortisol II or >400nmol/L for the Siemens assay) had a normal SST. Previous studies have reported that an early morning cortisol of >450nmol/L in the Siemens assay (8), >500nmol/L on the Roche cortisol I assay^{4-7,13} or >336nmol/L in the Abbott assay⁴ is strongly predictive of a normal SST response. We found that

Table 3: Indications on referral form for short synacthen tests. Data are N (%).

Indication	
No indication provided	57 (20)
Low basal cortisol	105 (37)
Symptoms of adrenal insufficiency	99 (34)
Prolonged treatment with corticosteroid	50 (17)
Electrolyte disturbance	12 (4)
Other*	19 (7.3)
Missing referral form	1 (0.3%)

*See text for description.

Total indications > 287 as some referrals included >1 indication.

64/287 (22%) of the SSTs performed were avoidable, based on a robust basal cortisol measurement, and conclude that obtaining a morning plasma cortisol result can assist the triage of patients who do not need a SST, facilitate prudent use of healthcare resources and reduce unnecessary testing for patients.¹³⁻¹⁵

Work from other groups has suggested that a morning plasma cortisol concentration less than 100nmol/L implies a very high probability of an abnormal SST response, making further testing unlikely to change management.^{4-11,13} Contrary to these reports, our audit suggests that a morning plasma cortisol below the reference range does not predict an abnormal SST with enough confidence to avoid proceeding to SST. Using a threshold of 100nmol/L did not improve the value of basal cortisol in predicting an abnormal SST.

We also identified that referrals for SSTs frequently lacked important information regarding current or recent use of corti-

costeroids, prior cortisol testing and the indication(s) for testing. These details are important both for interpretation of SST results and the determination of whether an SST is appropriate. For example, patients receiving long-term corticosteroid treatment at supraphysiological doses are likely to have an abnormal SST, and management is unlikely to change if an SST is undertaken. In only one in six referrals of patients who had had a plasma cortisol measurement was the numerical value provided. All 12 referrals from cardiology were for patients with postural hypotension or fatigue. Of these, only two had pre-test cortisol measurement and none had an abnormal SST.

An SST was sometimes requested when an alternative test may have been more appropriate. For example, some patients referred with inappropriate or unclear indications had also had either a dexamethasone suppression test or a 24-hour urinary free cortisol test performed recently, suggesting that there may have been confusion

Table 4: Basal cortisol and short synacthen test (SST) results by corticosteroid use. Data are N or N (%).

	No corticosteroid		Corticosteroid		
	N	Abnormal SST	N	Abnormal SST	
Total	172	4 (2)	115	29 (25)	
			PO/IM/IA	71	26 (37)
			Topical/inhaled	44	3 (7)
Cortisol measurement pre-SST					
Yes	125	4 (3)	69	12 (17)	
No	47	0 (0)	46	17 (37)	
Basal cortisol*					
robust ^a	39	0 (0)	25	0 (0)	
intermediate ^b	76	1 (1)	35	3 (9)	
low ^c	57	3 (5)	55	26 (47)	

PO, per oral; IM intramuscular; IA, intra-articular.

*Either cortisol measured pre-SST or 0 minute cortisol from SST.

a, >400 nmol/L Seimens assay; >300nmol/L Roche II assay.

b, 200–400 nmol/L collected 7am–10am or <200 nmol/L and collected after 10am Seimens assay; 170–300nmol/L collected 7am–10am or <170 nmol/L and collected after 10am Roche II assay.

c, <200 nmol/L collected 7am–10am Seimens assay; <170 nmol/L collected 7am–10am Roche Cortisol II assay.

between appropriate testing for cortisol excess and adrenal insufficiency.

This audit was conducted retrospectively and has some limitations. Details of use of corticosteroids were based in part on prescription data and enquiry on the day of the SST, rather than full medication histories, which may not accurately reflect the actual corticosteroid administration. We were unable to ascertain whether the SST results changed patient management. This is particularly pertinent with regards to those receiving long-term corticosteroid treatment. We excluded patients with known or suspected pituitary disease. The data were collected in an outpatient setting and may not apply to acute clinical settings.

In summary, an SST is often requested without clear indications and frequently with inadequate clinical information. A moderate proportion of tests could be avoided by measurement of single morning plasma cortisol. In order to permit determination as to whether the test is appropriate, referrals for SST should be accompanied by sufficient clinical information, in particular the indication(s) for testing and details regarding corticosteroid use and prior plasma cortisol results. A morning plasma cortisol should be mandatory before undertaking an SST, as a robust level makes further testing unnecessary. Adopting a structured request form that requires provision of the relevant information¹⁶ might improve the utility of SSTs.

Competing interests:

Nil.

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