

Standard Dose Synacthen Test for Suspected Adrenal Failure

Test Name: CHILD SYNACTHEN DFT

Principle

Adrenal glucocorticoid secretion is controlled by adrenocorticotrophic hormone (ACTH) released by the anterior pituitary. This test evaluates the ability of the adrenal cortex to produce cortisol after stimulation by synthetic ACTH (tetracosactrin: Synacthen). The Synacthen test is a useful investigation in suspected secondary adrenal insufficiency as it correlates reasonably well with the 'gold-standard' insulin tolerance test but is safer and less unpleasant. Chronic ACTH deficiency results in adrenal atrophy which leads to a reduced response to exogenous ACTH. A home waking salivary cortisone has been shown to be accurate in diagnosing adrenal insufficiency with comparability to the Synacthen test.

Indication

- Screening test for suspected adrenal insufficiency.

Precautions

- The Synacthen test is unreliable if performed within 4 weeks of pituitary surgery as ACTH deficiency may not have been sufficiently prolonged to result in adrenal atrophy. An 8 - 9 am plasma ACTH and cortisol can be informative in these situations.
- The test is unreliable in patients taking the oral contraceptive pill. Any oral oestrogen therapy should be discontinued for 6 weeks prior to performing the synacthen test.
- Do not perform this test at the same time as an oral glucose tolerance test. However, the oral glucose tolerance may be performed after the synacthen test.

Side Effects

- Severe allergic reactions to Synacthen have been described, particularly in children with a history of allergic disorders, but are very rare. In children with prior known synacthen sensitivity, a repeat synacthen test is not advisable. In such cases, morning basal ACTH and cortisol levels can alternatively test for adrenal function.

Preparation

Saliva Testing

On the day of the Synacthen test, a waking saliva sample is needed immediately after getting out of bed before brushing teeth, drinking/eating. Older children should be advised not to smoke or vape prior to the saliva sample.

Synacthen Testing

- The test should preferably be performed in the morning between 0800 and 0900 hrs.
- The patient does not need to be fasted once they have taken the saliva sample
- All glucocorticoid therapy (other than dexamethasone or betamethasone) interferes with the assay of cortisol. If the patient is on prednisolone therapy, this must be discontinued for 24 hours prior to the test. If the patient is on a supra-physiological dose of hydrocortisone, this should be reduced to a physiological level (6 micrograms/m²/day) prior to the test. Omit the dose the night before and on the morning of the test. If the paediatric endocrine consultant is very anxious about the degree of adrenal insufficiency, then omit only the morning hydrocortisone dose. However, the patient should take their usual dose of corticosteroid as soon as the test is completed.

Protocol

Saliva Testing

Patients are given Salivette tubes with a salivary collection swab or the longer SalivaBio swab with a standard 10 mL tube depending on their age. The Salivette are suitable for teenagers and the SalivaBio for younger children however, clinical judgement as to the competence of the individual child should be

used. Patients require written instructions/images on how to collect samples. On the day of the Synacthen test, a waking saliva sample is needed immediately after getting out of bed before brushing teeth, drinking/eating. Older children should be advised not to smoke or vape prior to the saliva sample. If using a Salivette tube, the collection swab should be chewed for 2 mins before sealing in the plastic tube for sending to the lab. If using the SalivaBio swab, about 2 cm should be put in the mouth and held at the end by either the child or a parent/legal guardian/hospital staff member. It takes about 2 mins to saturate the swab, after which it can be removed, cut to size and place in a standard 10 cm tube for sending to the lab. A flowchart of the process can be found in appendix 1.

Synacthen Testing

A number of different protocols with different synacthen doses are available. We have taken a pragmatic approach, considering the ease of use.

1. Insert a reliable cannula and, if possible, rest the patient for 30 minutes.
2. Collect an ACTH sample at baseline (if requested)
3. Take basal blood sample for cortisol (t = 0).
4. **Give Synacthen as an i.v. bolus**

Age	Generic	Brand (if applicable)	Route	Dose	Frequency	Comments
<1 month	Tetracosatide	Synacthen	i.v	36 micrograms/kg	Bolus	
1-12 months	Tetracosatide	Synacthen	i.v	125 micrograms	Bolus	Use 36 micrograms/kg for preterm babies who remain in hospital.
>1 year	Tetracosatide	Synacthen	i.v	250 micrograms	Bolus	

5. Take a blood sample at + 30 min after Synacthen for cortisol.

Samples

Cortisol 1.2 mL lithium heparin (orange top) or clotted blood (white top)

ACTH 1.8 mL EDTA tube (pink top)
Send IMMEDIATELY to laboratory on ice for centrifugation and freezing

Interpretation

Saliva Testing

- Waking salivary cortisone of <7nmol/L is consistent with adrenal insufficiency.
- Waking salivary cortisone of ≥17nmol/L is consistent with not being adrenal insufficient.
- Waking salivary cortisone levels between 7 and 16.9 nmol/L are equivocal and in these circumstances the Synacthen test result should be used on its own.

Synacthen Testing

Please note that synacthen test cut-offs vary from laboratory to laboratory and are dependent on the cortisol assay method. The MFT cut-off for both the Roche Gen II and LC-MS methods is 430 nmol/L. The table below displays cut-offs for other methods (El-Farhan et al., 2012) but please note new assay formulations which may require a change to the cut-off.

Method	SST cut-off
Siemens Centaur	446
Beckman Access	459
GC-MS	420
Architect	430
Immulite 2000	474

- A normal response is an increase in plasma/serum cortisol to a level of ≥ 430 nmol/L at 30 minutes.
- An impaired response does not distinguish between adrenal and pituitary failure, as the adrenal glands may be atrophied secondary to ACTH deficiency.
- The dose of Synacthen used is supra-physiological and may give a normal response in patients with mild adrenal insufficiency.
- The sensitivity of the Synacthen test is higher in primary adrenal insufficiency compared with secondary adrenal insufficiency. Sensitivity is particularly low in recent-onset ACTH deficiency (within 4 – 6 weeks of an insult to the pituitary).
- Cortisol results may be misleadingly low in the presence of low cortisol binding globulin (for example in severe illness, in conjunction with low albumin).
- In patients on long-term glucocorticoids, it is difficult to differentiate underlying adrenocortical disorders from the adrenal-suppressive effects of the treatment. A urine steroid profile may also be misleading after only 24 hours off hydrocortisone. The urine steroid lab at King's College Hospital recommends changing the glucocorticoid to dexamethasone and stimulating with depot Synacthen for up to 5 days before sample collection, unless glucocorticoid treatment has been brief. Please discuss with the paediatric endocrine team and the laboratory.

References

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3. Dorin R.I., Qualls C.R. & Crapo L.M. (2003) Diagnosis of adrenal insufficiency. *Ann Intern Med*. **139**: 194-204.
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5. Tonge JJ, Keevil BG, Craig JN, Whitaker MJ, Ross RJ, Elder CJ. Salivary Steroid Collection in Children Under Conditions Replicating Home Sampling. *The Journal of Clinical Endocrinology & Metabolism*, 2022, 107, 3128–3136.
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7. Debono M, Caunt S, Elder C, Fearnside J, Lewis J, Keevil B, Dixon S, Ross R. Real world evidence supports waking salivary cortisone as a screening test for adrenal insufficiency. *Clinical Endocrinology*, 2023, 99: 517–524.

Appendix 1: Saliva Collection Flowchart

- It is recommended to wait 30 min after eating, taking oral drugs or brushing teeth before collecting saliva
- Alternatively the sample may be taken on waking in the morning following getting out of bed and before these activities
- There should be no smoking or vaping before the test

