Standard Dose Synacthen Test for Suspected Adrenal Failure and Standard Dose Synacthen Test for Congenital Adrenal Hyperplasia (CAH)

Author: D Ismail, M Lazner, C Chadwick, T Cromwell. Adapted from Endocrine Dynamic Function Test Protocols for use in neonates and children – Manchester University NHS Foundation Trust November 2021 (H Beeston et al).

Approved by: UHS Medicines Governance Committee July 2022
Publication date: September 2022. Version 1
Review date: September 2024

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Standard Dose Synacthen Test for Suspected Adrenal Failure

Principles

- 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 (Tetracosactide (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.

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. If the patient is taking the oral contraceptive pill for contraception, advise discussion with the Sexual Health service or GP regarding alternative methods.

! Do not perform this test concurrently with an oral glucose tolerance test. However, the oral glucose tolerance may be performed **after** the Synacthen test, and can be same day, but **must not precede** the OGTT.

Side Effects

- Severe allergic reactions to Tetracosactide (Synacthen®) have been described, particularly in children with a history of allergic disorders, but are very rare.
- In children with prior known Tetracosactide (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

- The test should preferably be performed in the morning between 08:00 and 09:00.
- The patient does not need to be fasted.
- All glucocorticoid therapy (other than dexamethasone or betamethasone) interferes with the assay of cortisol.
  - If the patient is on prednisolone therapy, it must be discontinued for 24 hours prior to the test.
  - If the patient is on a supra-physiological dose of hydrocortisone, it should be reduced to a physiological level (6 mg/m^2/day) prior to the test. Omit the dose the night before and on the morning of the test. In cases of severe adrenal insufficiency, the paediatric endocrine consultant may advise that only the dose on the morning of the test is omitted.

Patients should take their usual dose of corticosteroid as soon as the test is completed.

Protocol

Time (mins)	Medication to be administered	Samples to be taken		
		Cap. blood glucose	Cortisol	ACTH
0		Yes	Yes	If requested by referring consultant
0	*Tetracosactide (Synacthen®)*			
30		Yes	Yes	
60		Yes	Yes	

1. Insert a 22G cannula and, if possible, rest the patient for 30 minutes.
2. Collect an ACTH sample at baseline (if requested by referring consultant)
3. Take basal blood sample for cortisol and capillary blood glucose (t = 0).
4. **Give Tetracosactide (Synacthen®) as an intravenous bolus**

   Doses: ***Age <1 month:*** *36 micrograms/kg*

   Age 1 – 6 months: *62.5 micrograms*

   Age 6 months - 2 years: *125 micrograms*

   Age >2 year: *250 micrograms*

5. Take blood samples at + 30 min and + 60 min after Tetracosactide (Synacthen®) for cortisol and capillary blood sugar.

Samples

Cortisol 1 mL clotted blood (yellow / gold top)
ACTH 1 mL blood in a 1.2 mL EDTA tube (pink top) ***Send IMMEDIATELY to laboratory on ice for centrifugation and freezing***

Record actual sample collection times on the printed labels.
SEND CORTISOL SAMPLES TO THE LABORATORY TOGETHER

Interpretation

Please note that Synacthen test cut-offs vary from laboratory to laboratory and are dependent on the cortisol assay method.

A normal response is an increase in plasma/serum cortisol to a level of ≥420 nmol/L at 30 minutes.

NB.

- 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 Tetracosactide (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 recommend changing the glucocorticoid to dexamethasone and stimulating with depot Tetracosactide (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.

Standard Dose Synacthen Test for Congenital Adrenal Hyperplasia (CAH) (Synacthen + 17-OHP)

Principles

- Adrenal glucocorticoid secretion is controlled by adrenocorticotrophic hormone (ACTH) released by the anterior pituitary.
- This test evaluates secretion of cortisol and 17-hydroxyprogesterone (17-OHP) by the adrenal cortex following stimulation with Tetracosactide (Synacthen®).
- In patients with congenital adrenal hyperplasia (CAH; a group of inherited disorders caused by enzyme defects in the steroid synthetic pathway), cortisol may, or may not, be adequately secreted. However, there is excessive secretion of the precursor steroids proximal to the defective enzyme.
- The commonest cause of CAH is due to 21-hydroxylase deficiency and in these children increased secretion of 17-hydroxyprogesterone (17-OHP) occurs.

Indication

Diagnosis of CAH due to 21-hydroxylase deficiency in children and adults.

Precautions

! The Synacthen test gives unreliable results if performed within 4 weeks of pituitary surgery.

! Do not perform this test concurrently with an oral glucose tolerance test. However, the oral glucose tolerance may be performed **after** the Synacthen test, and can be same day, but **must not precede** the OGTT

Side Effects

- Severe allergic reactions to Tetracosactide (Synacthen®) have been described, particularly in children with a history of allergic disorders, but are very rare.
- In children with prior known Tetracosactide (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

➲ The test should preferably be performed in the morning between 08:00 and 09:00.

➲ The patient does not need to be fasted.

➲ All glucocorticoid therapy (other than dexamethasone or betamethasone) interferes with the assay of cortisol.

- If the patient is on prednisolone therapy, it must be discontinued for 24 hours prior to the test.
- If the patient is on a supra-physiological dose of hydrocortisone, it should be reduced to a physiological level (6 mg/m2/day) prior to the test. Omit the dose the night before and on the morning of the test.

In cases of severe adrenal insufficiency, the paediatric endocrine consultant may advise that only the dose on the morning of the test is omitted.

Patients should take their usual dose of corticosteroid as soon as the test is completed.

Protocol

Time (mins)	Medication to be administered	Samples to be taken		
		Cap. blood glucose	Cortisol	17-OHP
0		Yes	Yes	Yes
0	***Tetracosactide (Synacthen®)***			
30		Yes	Yes	Yes
60		Yes	Yes	Yes

1. Insert a 22G cannula and, if possible, rest the patient for 30 minutes.
2. Collect an ACTH sample at baseline (if requested by referring consultant)
3. Take basal blood sample for cortisol, 17-OHP and capillary blood glucose (t = 0).
4. **Give Tetracosactide (Synacthen®) as an intravenous bolus**

   Doses: ***Age <1 month:*** *36 micrograms/kg*

   Age 1 – 6 months: *62.5 micrograms*

   Age 6 months - 2 years: *125 micrograms*

   Age >2 year: *250 micrograms*
5. Take blood samples at + 30 min and + 60 min after Tetracosactide (Synacthen®) for cortisol, 17-OHP and capillary blood sugar.

Samples

Cortisol and 17-OHP 2 mL clotted blood (yellow / gold top)
ACTH 1 mL blood in a 1.2 mL EDTA tube (pink top) ***Send IMMEDIATELY to laboratory on ice for centrifugation and freezing***

Record actual sample collection times on the printed labels.
SEND CORTISOL SAMPLES TO THE LABORATORY TOGETHER

Interpretation

- Unaffected adults and children usually have a basal 17-OHP of <6 nmol/L.
- A minority of patients with non-classical CAH have a normal basal 17-OHP, even on early morning samples.

- A normal response to Tetracosactide (Synacthen®) is a stimulated 17-OHP of <30 nmol/L at 60 minutes.

- A stimulated 17-OHP (60 minutes post-Tetracosactide (Synacthen®)) of 30 - 50 nmol/L is suggestive of CAH but some heterozygotes have levels within this range. Genotyping of the 21-hydroxylase gene may help reach a diagnosis.

- A stimulated 17-OHP of ≥50 nmol/L is consistent with a diagnosis of CAH.

- Milder elevations of 17-OHP may be found in rarer forms of CAH: 11-β-hydroxylase deficiency and 3-β-hydroxysteroid dehydrogenase deficiency.

- An increment of <10 nmol/L in normal individuals compared to >20 nmol/L in CAH has been reported.

- A normal cortisol response is an increase in plasma/serum cortisol to a level of ≥420 nmol/L at 30 minutes.

References

(adaptation with permission of authors: RMCH PAED ENDOCRINE and **Clinical Biochemistry** L Tetlow, B Hird , H Beeston**,** Prof I Banerjee, Dr A Chinoy , Prof P Clayton , Prof, Z Mughal , Dr P Murray , Dr R Padidela , Prof L Patel , Dr M Salomon Estebanez , Dr M Skae, E O'Shea).

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