Tetracosactide (Tetracosactrin) (Synacthen stimulation test)

2022

Newborn use only

Alert	Serum cortisol can be low at the time of hypoglycaemia in neonates with hyperinsulinemic hypoglycaemia (HH) and therefore should be interpreted with caution prior to proceeding with ACTH stimulation test (Synacthen test) in confirmed HH neonates.[1,2]
Indication	Investigation of suspected primary or secondary adrenocortical insufficiency. Assessment of possible adrenal suppression/atrophy due to steroid therapy.
Action	Diagnostic aid in assessment of suspected adrenocortical hypofunction. When administered, produces a marked rise in plasma cortisol.
Drug type	ACTH analogue. A synthetic polypeptide consisting of the first 24 amino acids of the ACTH molecule.
Trade name	Synacthen
Presentation	250 microgram/1 mL injection
Dose	**Standard dose Synacthen test (recommended)** 15 microgram/**kg** up to a maximum dose of 125 microgram.[3-5] **Low dose Synacthen test (only in consultation with and at the discretion of Paediatric Endocrinologist)** 1 microgram/**dose.**[6]
Dose adjustment	Not applicable
Maximum dose	125 microgram
Total cumulative dose	
Route	IV*[1,2,11] IM *The Australian product information states only IM, however the UK product information states IM or IV. In neonates, IV route is widely used in clinical practice. In newborns, it is not necessary to insert an IV cannula as repeated blood sampling is unreliable.
Preparation	**Standard dose Synacthen test** No dilution is required. **Low dose Synacthen test**[24] 1. Draw up 1 mL of 250 microgram/mL of Tetracosactide (Synacthen) and add 49 mL of sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 5 microgram/mL and mix well. 2. Take 1 mL of the above 5 microgram/mL solution and add 4 mL of sodium chloride 0.9% to make a 1 microgram/mL solution and mix well. 3. 1 microgram = 1 mL (irrespective of age or weight). Do not store solution for later use.
Administration	IV: Slow injection over 2 minutes.[11] IM: Inject into the anterolateral thigh (preferred) or the ventrogluteal areas. Depending on the volume, the dose may be given in 2 separate injection sites
Monitoring	Blood sampling performed via heel prick or venepuncture.

Sample	Tube/Volume	0 minutes (before Synacthen)	30 minutes	60 minutes
Cortisol	Lithium heparin 0.5 mL	Sample	Sample	Sample
ACTH	EDTA 1 mL	Sample		
17-OH progesterone*	Lithium heparin 0.5 mL	Sample*	Sample*	Sample*
Other adrenal steroids*		Sample*	Sample*	Sample*
Renin/angiotensin*		Sample*		

* If requested by the endocrinologist

Contraindications	Hypersensitivity reactions to ACTH treatment. Infections (unless antibiotics are being administered at the same time).

	Peptic ulcer. Cushing's syndrome. Heart failure (refractory). Current or recent treatment with corticosteroids.
Precautions	Synacthen should be used with caution in patients with diabetes mellitus or moderate to severe hypertension.
Drug interactions	Drug interactions of the type seen with steroids may occur
Adverse reactions	Hypersensitivity or anaphylactic reaction – rare. Full resuscitation facilities and drugs must be available.
Compatibility	Sodium chloride 0.9%, glucose 5%.
Incompatibility	No information
Stability	Infusion solution: Administer within 4 hours.[25]
Storage	Store between 2 – 8°C. Protect from light
Excipients	Acetic acid, sodium acetate, sodium chloride and water for injections
Special comments	• Sampling times and cut offs for the Synacthen test are not standardised and interpretation should be considered in light of this. • Frequently quoted thresholds are a peak cortisol of 500 or 550 nmol/L and a minimum cortisol rise from baseline of over 250 nmol/L. These thresholds may be too high with the current assays and the cut-off values depend on the method used by each laboratory. Examples are given below:

Cortisol assay (nmol/L)	Male and female not on OCP	
	Cut-off	Borderline zone
GC-MS	490	440-530
Siemen Centaur	520	470-570
Abbott Architect	500	450-550
Roche E170	490	440-530
Beckman Access	490	440-530
Siemen Immulite	550	490-600
Ortho Vitros	Children's Hospital Westmead (CHW, unpublished data) suggest values 20% lower than Siemen Immulite.	

• Interpretation of results should be based on the clinical scenario and consideration of the likelihood of adrenal insufficiency and desired sensitivity versus specificity.
• The dose of Synacthen used in the standard (250 microgram) test is supra-physiological and may give a normal response in patients with mild adrenal insufficiency. A low dose Synacthen test is thought to be more sensitive by some.
• Interpretation of other adrenal hormones in neonates, including 17OHP, should be done in consultation with an endocrinologist.
• Manufacturer recommends IM use only but has been widely used IV as well.[1,2]

Evidence

Adrenal insufficiency

Adrenal insufficiency (AI) may be caused by dysfunction or destruction of the adrenal gland (primary AI, Addison's disease), deficient pituitary adrenocorticotrophic hormone (ACTH) secretion (secondary AI), or deficient hypothalamic secretion of corticotropic releasing hormone (CRH) (tertiary AI). The secondary and tertiary AI can also be called central AI. The most common cause of primary AI in neonates is congenital adrenal hyperplasia (CAH) with 21-hydroxylase deficiency, accounting for ~ 90% of all CAH cases (incidence of 1 in 14,000 live births).[7] Bilateral adrenal haemorrhage can also cause primary AI.

Secondary AI secondary to intracranial pathology is rare and may be isolated deficiency of ACTH or CRH, or it may be part of other pituitary hormonal deficiencies, called hypopituitarism. Iatrogenic tertiary AI caused by suppression of the hypothalamic-pituitary adrenal (HPA) axis can occur after prolonged glucocorticoid therapy.[5]

In neonates, common indications for testing include postnatal exposure to exogenous glucocorticoids, midline defects, hypotension, hypoglycaemia, electrolyte disturbances (hyponatraemia/hyperkalaemia) and ambiguous genitalia.[11]

	Cortisol levels in newborns Random spot cortisol levels in newborn infants are often low and need to be interpreted in the context of the clinical presentation. At birth, mixed cord blood cortisol concentrations are relatively high (880 nmol/L); this reflects the maternal transfer of steroids and the stress of delivery. By 24 h of age, cortisol concentrations fall rapidly to about 270 nmol/L and by day 3 of life the normal cortisol values range between 46.9 and 385.4 nmol/L.[12,13] In very low birthweight infants, median basal serum cortisol was 167 nmol/L (IQR, 98-298 nmol/L). The basal serum cortisol concentration positively correlated with elapsed time from the last maternal betamethasone dose. Low serum cortisol concentration was associated with antenatal corticosteroid therapy, low lactic acid level and low leukocyte count at birth. Basal serum cortisol level was not associated with mortality and neonatal morbidities including hypotension and severe grade intraventricular haemorrhage.[14] Another prospective study in infants <28 weeks gestation showed a mean plasma cortisol 400.5 ± 42.6 nmol/L and the mean plasma ACTH 4.5 ± 0.9 pmol/L. Early morning plasma ACTH did not correlate with early morning plasma cortisol.[17] Newborns do not have a diurnal variation in cortisol secretion. Neonates with hyperinsulinemic hypoglycaemia (HH) fail to generate an adequate serum cortisol counter-regulatory hormonal response. This appears to be related to the lack of drive from the hypothalamic-pituitary axis, with inappropriately low plasma ACTH concentrations at the time of hypoglycaemia. This was demonstrated in 2 studies. Ahmed et al. found low serum cortisol (94.7 ± 83.1 nmol/L) and growth hormone (82.4 ± 29 m IU/L) at the time of hypoglycaemia in 9 neonates with HH. None of the HH infants in this study had cortisol levels >302 nmol/L at the time of hypoglycaemia. ACTH levels were also low (mean: 39.4 ± 20 pg/mL) during hypoglycaemia. However, a standard IV Synacthen test elicited a normal peak cortisol response (> 500 nmol/L) in these infants.[1] Similar findings were observed in a prospective study by Hussain et al. in 13 neonates with HH. The mean (± SEM) serum cortisol concentration 15 min before the hypoglycaemic episode was 156 ± 24 nmol/L, and at the time of hypoglycaemia was 182 ± 28 nmol/L. Plasma ACTH levels were also low at the time of hypoglycaemia. However, ACTH test elicited a normal peak cortisol response in them.[2] **Standard versus low dose Synacthen test** The standard dose 250 microgram ACTH stimulation (30 or 60 minutes) test has been modified for use in infants and children (15 microgram/kg for infants and 125 microgram for children <2 y of age)[3], although there are limited data reporting normal response ranges at these lower doses. Controversies exist in the literature surrounding the use of the different Synacthen stimulation tests in children. Both standard and low dose Synacthen tests when used in conjunction with clinical information are as effective in the assessment of central adrenal insufficiency in children. There is no clear evidence to indicate that one test is superior to another. The choice of test should be individualised based on clinical judgement for each patient and guided by a paediatric endocrinologist wherever possible.[6] Regarding timing of serum cortisol following Synacthen administration, the majority of neonatal cortisol peaks after low dose Synacthen occurred at the 60-minute sampling time with the addition of a 30-minute sample providing substantial benefit.[11]
Practice points	
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