

Insulin Tolerance Test - Full Clinical Guideline

(Document Code: CHISCG36)

**THIS TEST IS ONLY TO BE PERFORMED FOLLOWING DISCUSSION
WITH A CONSULTANT BIOCHEMIST OR ENDOCRINOLOGIST**

1. Introduction

The Insulin Tolerance Test is considered the 'Gold Standard' investigation to assess the Hypothalamo-Pituitary-Adrenal axis as well as Growth Hormone (GH) reserve.

In terms of assessing the hypothalamo-pituitary-adrenal axis the 9am Short Synacthen test is often sufficient. The short synacthen test is not appropriate for use for at least 6 weeks following an acute pituitary insult (such as hypophysectomy or apoplexy). If assessment is required during that time the Insulin Tolerance test is needed. The Insulin Tolerance test may also be indicated in assessment of this hormone axis when the Short Synacthen test shows a borderline or unexpected result.

In order to receive NHS funded Growth Hormone therapy patients must have severe growth hormone deficiency defined as;

- Known hypothalamic pituitary abnormality
- Known deficiency of at least one other pituitary hormone
- AGHDA questionnaire score of at least 11 despite adequate replacement of all other hormone deficiencies
- Peak growth hormone of less than 3 µg/L on insulin tolerance test (or equivalent other test if contraindicated)

Therefore, the Insulin Tolerance test for Growth hormone deficiency should only be performed in those patients who would meet all other criteria for treatment.

When performing the test it is usual to assess both hormone systems simultaneously to reduce the need for retesting at a later date.

2. Guideline

INDICATIONS

The assessment of ACTH/cortisol and GH reserve

CONTRAINDICATIONS

Ischaemic heart disease

Epilepsy or unexplained blackouts

Severe panhypopituitarism, hypoadrenalism (9am cortisol <100nmol/L) - Untreated

Untreated hypothyroidism (low FT4)

Hypocalcaemia or Hypokalaemia until corrected

Glycogen Storage Disease or BMI <18 if poor liver glycogen stores are suspected

SIDE EFFECTS

Hypoglycaemia is an intrinsic part of the investigation and can precipitate cardiac ischaemia, arrhythmia or seizure in susceptible patients.

PRECAUTIONS/ PRETESTING

- ECG must be normal, ideally on the day of the ITT (within 3 months if low risk for and asymptomatic of cardiac ischaemia)
- Serum cortisol (09:00) must be above 100 nmol/L (unless patient already established on glucocorticoid replacement)
- If the patient is on steroid replacement therapy, the referring endocrinologist must clarify their plan to omit (if testing Hypothalamo-Pituitary-Adrenal axis), or increase (if testing Growth Hormone (GH) reserve) treatment prior to the test
- Serum FT4 must be normal - replace first if low
- Ensure electrolytes are replaced to within normal ranges

Alternative tests depend on which hormone axis is primarily of interest. For growth hormone the best alternative is the GnRH/arginine test, or the Glucagon Stress Test

PREPARATION

Planning

- Please print and use the monitoring sheet (pg 6&7 of this guideline) to record the test

The SpR must be contacted regarding the date of the test and must consent the patient. They should also be present throughout the test. This procedure requires insertion of two indwelling venous cannulas and requires medical supervision in case of problems. 10% dextrose (500mls) and 20% dextrose (100mls) and i.v. hydrocortisone 100mg ampoules should be available and prescribed as PRN.

Patient

The patient should have a normal diet (containing at least 150g carbohydrate per day) for at least three days prior to the test. The patient should fast from midnight prior to the test, **and not smoke, eat or drink anything except water until the test is completed.** The patient should be at rest before and during the test.

The patient should be weighed before the start of the test.

Equipment

- Soluble insulin - give insulin Actrapid intravenously;
Usual dose: 0.15 U/kg stat IV
Type 2 Diabetes, Cushing's and Acromegaly: 0.3 U/kg stat IV
[Type 2 Diabetes with BG >11.1mmol/L: Start IV insulin infusion at 0.3U/kg/hr, checking venous blood glucose every 10mins until BG <9.0mmol/L. Then stop infusion and give appropriate IV stat dose.]
- Specimen tubes required:
2 Indwelling venous cannulas
6-8 SST tubes (Yellow Top)
6-8 fluoride oxalate tubes (Grey top)
- Hypoglycaemia and adrenal crisis treatment
500ml of 10% dextrose ready for IV infusion, with 100mls 20% Dextrose ready as a bolus
IV hydrocortisone 100mg ampoules (stat) and 1L 0.9% Saline infusion available for infusion.
4x Orange Juice Cartons OR other oral hypoglycaemic treatment

PROCEDURE

Growth hormone and cortisol are stress hormones and it is therefore important that the patient must be rested throughout the procedure and that the protocol is followed properly.

Use one cannula for sample collection and one for infusion of i.v. insulin (and dextrose / hydrocortisone if required). The procedure ends after either 120 min or 150 min, depending on whether a second dose of insulin is required, as described in table below. Samples must be labelled clearly with patient name, date and **time** of sampling.

TIME	BLOOD SAMPLE
All time points glucose (Grey top) and GH/Cortisol (Yellow top)	
Weigh patient. Insert two venous cannulas and allow patient to rest for 30 min before taking first blood sample. Samples collected at intervals as follows:	
0 minutes	8 mL blood: 6mL into SST (yellow top) 2mL in fluoride oxalate (grey top) tube
<p>Immediately after time zero sample give iv Insulin via the second cannula (see dose details above).</p> <ul style="list-style-type: none"> • Measure near-bedside venous blood glucose levels every 5-10 minutes and record on the monitoring sheet and observe pulse for signs of hypoglycaemia • Once hypoglycaemia achieved perform near-bedside venous glucose every 10-20mins once recovered • If not clinically hypoglycaemic (sweating, tachycardia) at 45 min or if bedside glucose not <2.5 mmol/L, then consider repeating insulin dose in full • Record time of hypoglycaemia on Pathology form and monitoring sheet <p>Sampling times (one insulin dose): 0, 30, 45, 60, 90 and 120 min as below. If insulin dose repeated*, sample at 0, 30, 45*, 60, 75, 90, 105, 120 and 150 min. The patient must be awake throughout and be able to answer simple questions.</p>	
+ 30 minutes	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
45 minutes	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
60 minutes	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
75 minutes (only if additional insulin dose given)	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
90 minutes	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
105 minutes (only if additional insulin dose given)	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
120 minutes	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
150 minutes (only if additional insulin dose given)	6 mL in SST (yellow top) and 2 mL in fluoride oxalate tube (grey top)
Lunch and a sweet drink (e.g. orange juice) should be given at the end of the test. Observe for 2hr after the end of the test.	

Send all samples together with a completed Chemical Pathology request form, to the laboratory. Request should be for glucose, growth hormone and cortisol (only if testing), and should state that it is an Insulin Tolerance Test.

RESCUE

With severe and prolonged hypoglycaemia (over 20 min), or impending or actual loss of consciousness, or fits; terminate the hypoglycaemia by giving bolus of 100mL of 20% dextrose iv followed by an infusion of 10% Dextrose at 200ml per hour but then take ***an immediate additional blood sample, noting the time and continue sampling as per protocol if the patient is well enough***- the hypoglycaemic stimulus was achieved.

Consider hydrocortisone 100mg i.v. bolus in three situations;

- anytime, alongside iv 0.9% Saline if acute adrenal crisis is suspected (hypotension, vomiting) and abort the test
- at end of test if unwell
- for refractory hypoglycaemia (No recovery 30 minutes after profound hypoglycaemia)
 - regardless of point in protocol if GH alone being tested and ***continue sampling as per protocol if the patient is well enough***
 - regardless of point in protocol if both cortisol and GH being tested, but take a cortisol sample first and ***continue sampling as per protocol only for GH if the patient is well enough***

INTERPRETATION

Adequate test:

Blood glucose: must fall to <2.2 mmol/L, as tested by the laboratory, for an adequate and reliable stimulus to have been delivered. If adequate hypoglycaemia was not achieved then cortisol or GH deficiency cannot be diagnosed but a normal response still indicates adequate reserve.

Implications of cortisol results:

Normal response is defined as a maximal serum cortisol concentration of greater than 420 nmol/L.

Patients with just subnormal maximal serum cortisol responses but normal 0min cortisol value may not require regular replacement therapy but do require cover for major illness and surgery; they should be informed of this and carry a steroid card and/or MedicAlert.

All other patients with subnormal responses require steroid replacement therapy and full 'steroid education'.

Untreated hypothyroidism can also give subnormal results.

Implications of GH results:

In a normal response Growth Hormone rises to above 13 micrograms/L (6.5 - 13 micrograms/L equivocal) but this is very different from the definition of severe growth hormone deficiency used by NICE to define the patient group requiring treatment (see <https://www.nice.org.uk/Guidance/TA64>).

In order to receive NHS funded Growth Hormone therapy patients must have severe growth hormone deficiency defined as;

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Reassessment of AGDHA after 9 months of appropriately titrated growth hormone therapy should show an improvement of 7 marks in order for treatment to continue.

TURNROUND TIME

Glucose and cortisol results are available within one working day. Growth hormone results may take up to 3 weeks.

3. References

Barts Endocrine Protocols

4. Documentation Controls

Reference Number CHISCG34	Version: 6.0.0		Status Final	Authors: Specialist Healthcare Science Practitioner (Helen Seddon) Consultant Endocrinologist (Antonia Ugur)
Version / Amendment History	Version	Date	Authors	Reason
	6.0.0	Aug 2023	Helen Seddon, Antonia Ugur	Review in consultation with Departments of Biochemistry and Endocrinology
Intended Recipients: Endocrinology (medics and nurse specialists) and Biochemistry staff				
Training and Dissemination: Guideline reviewed and agreed at the monthly Biochemistry/Endocrine MDT meeting. All relevant staff are aware of this guideline.				
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Keywords: Insulin, growth hormone				
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Date of Upload			Sept 2023	
Review Date			Sept 2026	
Contact for Review			Consultant Healthcare Scientist (Julia Forsyth) Specialist Healthcare Science Practitioner (Helen Seddon)	

INSULIN STRESS TEST MONITORING SHEET

Date.....

Patient ID Sticker

- **Insert X 2 Venous Cannula**; allow patient to rest for 30 mins before taking 1st sample (1 grey for **glucose**, and 1 yellow for **GH and Cortisol**)
- Check Weight
- Perform ECG (Seen by Registrar Yes/ No). OK to proceed Yes/ No
- ConsentYes/No
- Recent Cortisol level (Date/ Result.....)
- On Glucocorticoid Yes/No Dose last taken Timing..... Amount.....
- Recent T4 level (Date...../ Result.....)

	Actual Time	Action/ Samples	Venous Nearside Glucose	Lab Gluc	Symptoms/Comments
-30 mins		Insert cannulas			
0 mins		Take bloods: 1 yellow for GH and cortisol & 1 Grey for Glucose Give IV Insulin			
+ 5 mins			*		Pulse
+ 10 mins			*		Pulse
+ 15 mins			*		Pulse
+ 20 mins			*		Pulse
+ 25 mins			*		Pulse
+ 30 mins		Take bloods for GH / Cortisol and Glucose (grey and yellow)			Pulse
+ 35 mins			*		Pulse
+ 40 mins			*		Pulse
+ 45 Mins		As above If not clinically hypoglycaemic or if bedside glucose not <2.5 mmol/L, consider repeating insulin dose in full	*		Pulse
+ 50 mins			*		Pulse
+ 55 mins			*		Pulse
+ 60 Mins		As above	*		Pulse
+ 65 mins			*		Pulse
+ 70 mins			*		Pulse
+75 mins		As above	*		Pulse

only if additional insulin given)					
+ 90 mins		As Above	*		Pulse
+105mins only if additional insulin given)		As Above	*		Pulse
+120 mins		As Above	*		Pulse
+150 mins only if additional insulin given		As Above	*		Pulse