Insulinoma - 72 hour Fast Protocol - RNS Endocrinology

Test name
72 hour fast

Alternate test names

Related Tests
Mixed meal test

Indication(s)
Differential diagnosis of causes of hypoglycaemia.

Hypoglycaemia is rare in persons who do not have drug-treated diabetes mellitus. Investigation of hypoglycaemia with a 72 hour fast is reserved for those patients with documented hypoglycaemia as defined by Whipple’s triad:

- Symptoms consistent with hypoglycaemia
- A low plasma glucose concentration measured with a precise method (not a glucose monitor)
- Relief of those symptoms after the plasma glucose level is raised

A 72 hour fast in patients not documented to have Whipple’s triad will very likely expose patients who do not have a specific pathology causing hypoglycaemia to unnecessary evaluations, costs, and potential harms without expectation of benefit.

Background
Clinical hypoglycaemia is a plasma (or serum) glucose concentration low enough to cause symptoms and/or signs, including impairment of brain function. The clinical manifestations of hypoglycaemia are nonspecific, it is not possible to state a single plasma glucose concentration that categorically defines hypoglycaemia.

When the cause of the hypoglycaemic disorder is not evident, i.e. in a seemingly well individual, laboratory testing can help to distinguish between possible causes. Ideally samples would be taken during a spontaneous episode of hypoglycaemia and after administration of glucagon.
When a spontaneous hypoglycaemic episode cannot be observed, it is often appropriate to formally recreate the circumstances in which symptomatic hypoglycaemia is likely to occur, i.e. during a fast of up to 72 hours.
Causes of hypoglycaemia in adults

Ill or medicated individual

1. Drugs
   - Insulin or insulin secretagogue
   - Alcohol
   - Others

2. Critical illnesses
   - Hepatic, renal, or cardiac failure
   - Sepsis (including malaria)
   - Inanition

3. Hormone deficiency
   - Cortisol
   - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)

4. Nonislet cell tumor

Seemingly well individual

5. Endogenous hyperinsulinism
   - Insulinoma
   - Functional b-cell disorders (nesidioblastosis)
   - Noninsulinoma pancreatogenous hypoglycaemia
   - Post gastric bypass hypoglycaemia
   - Insulin autoimmune hypoglycaemia
   - Antibody to insulin
   - Antibody to insulin receptor
   - Insulin secretagogue
   - Other

6. Accidental, surreptitious, or malicious hypoglycaemia

Table copied from Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728 – “Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline”

Interpretation

Patterns of findings during prolonged fasting

<table>
<thead>
<tr>
<th>Symptom s and/or signs</th>
<th>Glucose mmol/L</th>
<th>Insulin mIU/L</th>
<th>C-peptide pmol/L</th>
<th>Proinsulin pmol/L</th>
<th>β-Hydroxybutyrate mmol/L</th>
<th>Glucose increase after glucagon mmol/L</th>
<th>Circulating oral hypo- glycaemic</th>
<th>Antibodies to insulin</th>
<th>Diagnostic interpretation</th>
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<td>&gt; 1.4</td>
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Neg, negative; Pos, positive; NIPHS, noninsulinoma pancreatogenous hypoglycaemia syndrome; PGBH, post gastric bypass hypoglycaemia.
Precautions/Contraindications
Hypoglycaemia may exacerbate other conditions in patients with medical comorbidities. Hypoglycaemia in otherwise healthy patients may cause severe symptoms including seizures and loss of consciousness. Profound, prolonged hypoglycaemia can cause brain death.

Before the test is requested a clinical evaluation must be made to ensure the test will be safe and appropriate for each individual patient.

Patient Preparation
Patients must be explained the procedure in full and consented.
All nonessential medications should be discontinued.
Date the onset of the fast as the time of the last food intake.
Because of the expected long duration of the test, patients should be admitted to hospital.

Equipment
- Blood sample tubes
  - ~15 x 4mL Serum separator clot activator tubes (red top, yellow centre) for insulin/proinsulin/C-peptide
  - ~20 x 2mL Sodium fluoride/potassium oxalate (grey top, white centre) tubes for glucose
  - ~15 x 5mL Pre-chilled 5% perchloric acid (specially weighed tube from express biochemistry) for beta-hydroxybutyrate
  - No gel clot tube + Clot Activator tube (red top, black centre) for sulphonylurea screen
- Point of care glucometer
- Ice for beta-hydroxybutyrate
- Glucagon 1mg for intravenous injection
- Food for patient to end the fast

Procedure
Date the onset of the fast as the time of the last food intake.
Allow the patient to drink calorie-free and caffeine-free beverages.
Ensure that the patient is active during waking hours.
On admission to hospital the patient should have an IV cannula sited for administration of glucagon and IV dextrose if required.
This procedure occurs over 72 hours and therefore requires co-operation across multiple shift work cycles. It is important that there is clear documentation of the purpose and procedure of the test in the patient’s notes. Just as important is a clear handover of the patient to each afterhours shift.

The patient is reviewed and blood samples are collected every 2 – 6 hours until the fast is ended.

**Routine Review Cycle:**
1. Collect free flowing blood samples (no tourniquet) for
   - plasma glucose,
   - insulin, C-peptide, proinsulin, and
   - b-hydroxybutyrate.
2. Ask the patient about symptoms and signs of hypoglycaemia and document any present.
3. Do a finger prick BSL.
4. Allocate the time for the next review cycle
   - 2 hours later if BSL < 3.3mmol, otherwise 6 hours later.
5. Send samples to the labs.
   - Write on the request form: “Please measure plasma glucose concentration first. Then only go on to analyse insulin, C-peptide, and proinsulin if plasma glucose concentration is less than 3.3 mmol/L.”

**Review for symptoms:**
If the patient develops symptoms of hypoglycaemia, make a clinical assessment of the patient. Document the signs and symptoms present. If it is judged necessary to treat urgently because of severe symptoms, obtain samples for all of the following before administering carbohydrates.

Collect free flowing blood samples (no tourniquet) for plasma glucose, insulin, C-peptide, proinsulin, b-hydroxybutyrate and sulphonylurea screen.

**Criteria to end the fast:**
- The laboratory measured plasma glucose concentration is less than 2.5 mmol/L
  - **AND** the patient has symptoms and/or signs of hypoglycaemia
    - Ending the fast should not be based on a low plasma glucose concentration alone, in the absence of symptoms or signs, because some healthy individuals, especially women and children, have low glucose levels during prolonged fasting.
- The plasma glucose concentration is less than 3.0 mmol/L without symptoms or signs but Whipple's triad has been documented unequivocally on a prior occasion.
- 72 hours have elapsed without symptoms

**Ending the fast**

These steps are performed when the fast is ended:

1. Document the time and collect samples for
   a. Plasma glucose (Sodium fluoride/potassium oxalate tube)
   b. Insulin, C-peptide, proinsulin (Serum separator clot activator tube)
   c. BHOB, (5% perchloric acid tube on ice)
   d. Oral hypoglycaemic agents (No gel clot activator tube) – **make sure to collect this extra tube not collected in the routine review cycle**

2. Give 1 mg of glucagon intravenously. Note this in the comments section of the form.

3. Collect blood to measure the plasma glucose (Sodium fluoride/potassium oxalate tube)
   a. 10 minutes later
   b. 20 minutes later
   c. 30 minutes later

4. The patient is fed
72 Hour Fast – Royal North Shore Hospital

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<th>Time:</th>
<th>Finger prick BSL</th>
<th>Laboratory BSL</th>
<th>Bloods tubes collected</th>
<th>Symptoms and signs</th>
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