Improving the “gold standard”. The insulin tolerance test (ITT) revisited.

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Background

The ITT is regarded as the gold standard for diagnosing Growth Hormone deficiency (GHD) for 50 years.

Roth et al (1963) demonstrated the GH response to insulin-induced hypoglycaemia in 6 healthy adults and insulin-induced hypoglycaemia as a “specific, sensitive and direct test of pituitary somatotropic function”.

The selection of 0, 20, 30, 60, 90 and 120 min time points was sufficient according to the author to determine the near maximum GH values based on 5 minute sampling in a subgroup of only 3 participants.

These time points are still used with minor variations in many protocols worldwide.

Objectives

To evaluate the impact of alternative sampling time points to the specificity of the test.

Participants & Methods

Results from all paediatric ITTs using two different sampling protocols were extracted from the departmental database:

- **Protocol sITT (Standard ITT)** with time points: -30, 0, 30, 60, 90, 120 min and
- **Protocol rITT (Revised ITT)** with time points: -30, 0, 20, 30, 45, 60, 75, 90 min.

GH deficiency (GHD) was defined by peak GH <7mcg/l for paediatric or <5mcg/l in transition age.

The ITT was performed in accordance to the local paediatric endocrine department protocol by administering soluble insulin i.v. (Actrapid, Novo Nordisk, Denmark) at a dose of 0.15 U/kg or 0.10 U/kg if there were concerns of multiple pituitary hormone deficiency.

Patients were fasted overnight and were not on any steroid containing medication.

Serum glucose was determined every 5-10 min for the first 30 min and every 15 min thereafter. A successful test was defined by a blood glucose nadir lower than 2.2 mmol/l or clinical symptoms of hypoglycaemia.

Serum GH concentrations were measured using a commercial immunoassay (“hGH”, Roche Diagnostics GmbH) on a Cobas e601 immunoassay analyser.

Ten ITT protocols from other UK centres were reviewed and compared.

Results

Results from 645 tests between 2009-2016 were extracted.

Exclusion criteria:

- tests with two or more missing samples (n=40) and
- unsuccessful tests (no hypoglycaemia, n=9 [2%])

The remaining 596 ITT tests (314 with sITT and 282 with rITT) were included for further analyses.

The glucose nadir occurred at 15 or 20 minutes in 80% of tests and at 30 minutes in the remaining 20%. There was one incident of hypoglycaemic seizure that resolved with administration of i.v. glucose in a patient without a history of epilepsy.

Highest GH levels were measured at 60 minutes on sITT but at 45 minutes on rITT.

Abnormal results were seen in 85% (268/314) of sITT and 90% (253/282) of rITT but the difference was not statistically significant (Fisher’s exact test p=.07).

- The minus 30 min sample precluded GHD (i.e. was the highest level of GH during the test and the only one that precluded GHD) in 17% of all normal tests. This was more evident with the rITT (31%) vs sITT (9%) (Fig 1,2)
- By using the same criteria, GHD was precluded with the 45 min sample in 34% (10/29) of normal rITT.
- The 20 and 75 min sample precluded GHD in only 6% (2/29) rITT .
- The 90 and 120min sample did not preclude GHD in any test (sITT or rITT).

Fig 1

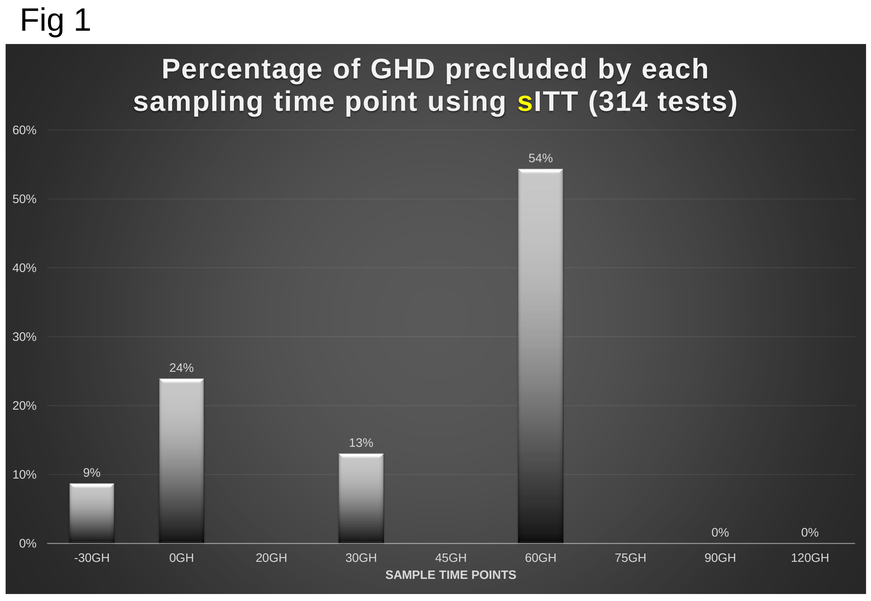
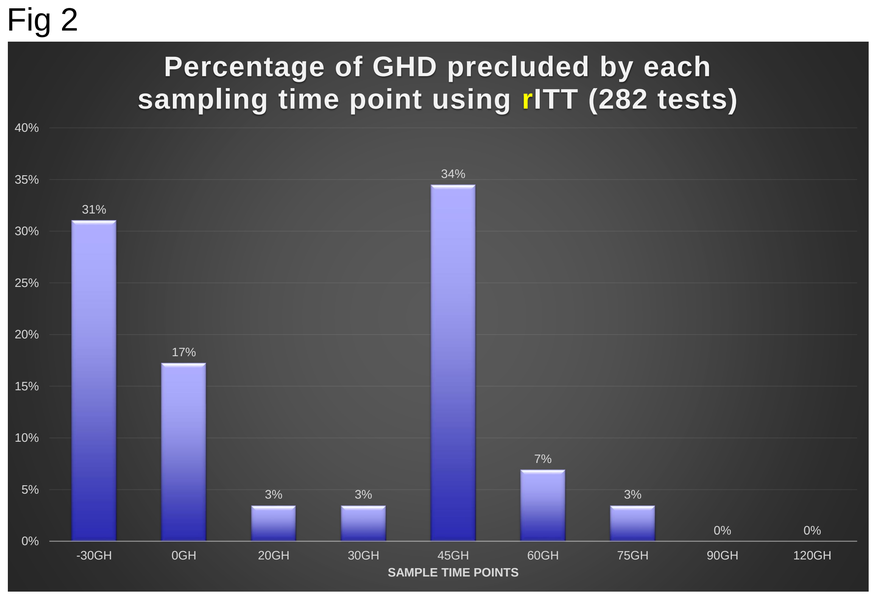


Fig 2



Conclusions

- GH levels that preclude GHD can be seen at minus 30 minutes (i.e. even before administration of insulin) in 2% of children having ITT and represents the highest level in 17% of normal tests.
- 45 and to a much lesser extent 75 minute samples can preclude GHD deficiency in an **additional 4%** of children having ITT avoiding potentially inappropriate and costly GH treatment or repeat tests.
- 90 and 120 min sampling did not preclude GHD diagnosis and can be omitted from ITT protocols.

Recommended sampling points: -30, 0, 20, 30, 45, 60

References

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Growth

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