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Saira Waqar Lone
National Institute of Child Health

Yasir Naqi Khan
National Institute of Child Health

Farah Qamar
Aga Khan University

Irum Atta
National Institute of Child Health

Mohsina Noor Ibrahim
National Institute of Child Health

See next page for additional authors

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Authors

Saira Waqar Lone, Yasir Naqi Khan, Farah Qamar, Irum Atta, Mohsina Noor Ibrahim, and Jamal Raza

Original Article

Safety of insulin tolerance test for the assessment of growth hormone deficiency in children

Saira Waqar Lone,[1] Yasir Naqi Khan,[2] Farah Qamar,[3] Irum Atta,[4] Mohsina Noor Ibrahim,[5] Jamal Raza[6]

Department of Paediatrics, National Institute of Child Health,[1,2,4-6] Aga Khan University Hospital,[3] Karachi.

Abstract

Objective: To determine the safety of insulin tolerance test (ITT) for assessing growth hormone (GH) deficiency in children.

Methods: This hospital based study was conducted at the National Institute of Child Health, Karachi from 1st November 2008 till 30th October 2009. All children suspected of growth hormone deficiency, were included after excluding all other causes of short stature. Verbal informed consent was taken from the parents. Children less than 2 years of age, weighing less than 10 kg, untreated/ inadequately treated hypothyroidism or Addison's disease, epilepsy, having history of hypoglycaemic fits or cardiac disease were excluded. All children were subjected to the international standard protocol of ITT and their samples of growth hormone and blood sugars were drawn. Complications during the procedure like hypoglycaemia, hypothermia, loss of consciousness, fits, vomiting and failure to achieve hypoglycaemia were recorded. Insulin tolerance test was performed on a total of 168 subjects. The data was entered in SPSS version 17 for analysis.

Results: A total of 168 children were subjected to the ITT. Four of them were abandoned as they could not achieve hypoglycaemia despite repeating the dose of insulin. Results were analyzed on 164 children whose mean age was 10 ± 3.5 years. There were 96 (58%) males and 68(41%) females. Over all 79.8% children achieved hypoglycaemia. None of the subjects developed any complication (fits, loss of consciousness,) or required intravenous glucose during the test and it was completed in all children with close monitoring. The results showed that there was a significant effect of time after insulin administration on both the blood glucose level (BG) and growth hormone (GH) levels. The blood glucose level decreased rapidly after administration of insulin and was lowest 30 minutes after injection and showed an increasing trend in subsequent readings, becoming almost equal to the baseline value 120 min after injection. From the study group 111 (66%) children were diagnosed as having growth hormone deficiency, 52 (31.3%) were normal and 1(0.6%) had growth hormone insensitivity.

Conclusion: ITT in children was found to be a safe and reliable test but can be potentially dangerous and requires very close monitoring and supervision and should be performed in a center with experienced staff.

Keywords: Insulin tolerance test, hypoglycaemia, growth hormone deficiency (JPMA 61:153; 2011).

Introduction

The exact incidence of growth hormone deficiency (GHD) in children is unknown; several studies estimate it to range between 1 per 4,000 to 1 per 10,000 children presenting with short stature.[1] Children with growth hormone deficiency present in the neonatal period with hypoglycaemia, prolonged jaundice and micropenis. In childhood the presentation is with short stature, slowing of growth (decreased growth velocity) and delayed puberty. The diagnosis of growth hormone deficiency in children is complicated requiring both clinical and laboratory investigations and is a challenging task. The pulsatile nature of growth hormone secretion causes a random measurement of serum growth hormone which is not helpful in the diagnosis of growth hormone deficiency.[2,3] Provocative tests are needed to evaluate the growth hormone reserve and the commonly used ones are; Insulin induced hypoglycaemia (ITT), clonidine stimulation, arginine stimulation, glucagon, growth hormone releasing hormone stimulation tests and two abnormal tests are used to confirm impaired GH secretion.[4]

There is unfortunately no consensus in children regarding the gold standard test for diagnosis of growth hormone deficiency. The commonly used tests in children are ITT, L-dopa and clonidine. The ITT has been shown to be safe in children when performed following an international protocol in experienced centers with strict observation for side effects. Galloway et al in his large review of 10 years data regarding the safety of ITT reported no serious side effects during the test.[5]

In adults the ITT has been considered as the gold standard in assessing growth hormone and cortisol reserve.[4] An audit of ITT in adults by Lange et al showed that no serious side effects occurred during it and concluded it to be a safe test when performed in experienced hands.[6]

The exact incidence of growth hormone deficiency in our country is unknown but small scale studies in children with short stature have been conducted and show it to range between 6.1% and 14%.[7,8] A local study in which ninety nine children were subjected to ITT, 47 were found to be growth hormone deficient.[9] Because of the lack of a gold standard, various tests are being used in our country but local data regarding the safety of these tests are not available.

There is a pediatric endocrine clinic at the National Institute of Child Health which caters to endocrine problems of children from all over the city. ITT is regularly performed in this hospital for the diagnosis of GH deficiency but safety of the test in the local population has not been established. The study was undertaken to establish the safety of ITT for the diagnosis of growth hormone deficiency in our population.

The outcome measures used were complications occurring during the test as a result of hypoglycaemia.

(seizures, loss of consciousness) requiring administration of glucose.

Material and Methods

This study was conducted at National Institute of Child Health, Karachi from 1st December 2008 till 1st December 2009.All children suspected of growth hormone deficiency were included. Those children who were less than 2 years of age, weighed less than 10 kg, untreated/ inadequately treated hypothyroidism or Addison's disease, epilepsy, hypoglycaemic fits or cardiac disease were excluded. The ITT was performed according to the standard international protocol after taking consent from parents. The test was carried out in the presence of a doctor and a trained staff nurse. The child on whom the test was to be performed was admitted on the evening prior to the test and fasted over night and only water was allowed. Rapid acting insulin, glucometer with strips, 10% dextrose water and injection hydrocortisone 100mg were present at the bedside at the time of the test. The child was told to bed rest for 30 min before the test. A large bore intravenous cannula was inserted which was connected to an extension tube for repeated sampling.

The blood glucose was checked at baseline via a glucometer and rapid acting insulin given at a dose of 0.1IU/kg intravenously and all the blood glucose during the ITT were checked on glucometer. Blood samples for serum blood glucose and serum growth hormone were drawn at 0, 30, 60, 90 and 120 minutes and sent to the laboratory.

If the blood glucose at baseline was less than 45 mg/dl, no insulin was given and the next sample of 60 min drawn. If blood glucose was less than 40 mg/dL, then a glucose drink with a volume of 30 mI was given. If blood glucose did not increase within 30 minutes or further decreased, a further 30 ml was given orally. If the child could not tolerate oral glucose then intravenous glucose 200 mg/kg (10% dextrose, 2 ml/kg) over 3 minutes was given. If panhypopituitarism was suspected (for example in children who had radiotherapy) 100 mg of hydrocortisone was administered intravenously as a bolus. Following the test the child was provided a meal and discharged from the hospital only after an adequate meal had been taken, and the blood glucose was at least 72mg/dL.

The procedure of ITT is as follows:

1. At 0 minute: Check blood glucose, if less than 45 mg/dl, no insulin is given. If blood sugar> 45mg/dl, 0.01u/kg of intravenous insulin is given. Draw samples of blood glucose and Growth hormone(GH) for laboratory,

2. 30 minutes: Check blood glucose and collect samples of blood glucose and GH for laboratory.

3. 60 minutes: Check blood glucose and collect samples of blood glucose and GH for laboratory.

4. 90 minutes: Check blood glucose and collect samples of blood glucose and GH for laboratory.

5. 120 minutes: Check blood glucose on glucometer and collect samples of blood glucose and GH for laboratory. Allow the child orally. Keep him under observation for 4 hours and then discharge.

Hypoglycaemia was defined as blood glucose of less than 45 mg/dl, but some children developed clinical hypoglycaemia (sweating) and their samples were drawn at that time even if blood glucose was not less than 45 mg/dl. Growth hormone deficiency was diagnosed if the value of peak serum growth hormone was less than 10 µg/l and value above 10 µg/l excluded growth hormone deficiency.

The samples for serum blood glucose were analyzed by biochemistry auto analyzer on Dimension RxL and serum growth hormone was analyzed by ELISA on Immulite 1000 at the laboratory at National Institute of Child Health.

Statistical analysis:

The mean and standard deviation of age, blood glucose levels and growth hormone measured at 30 minute intervals during the ITT were calculated. The frequency of children developing hypoglycaemia (blood sugar <45 mg/dl) was calculated.

The serial levels of blood glucose and growth hormone at baseline, 30, 60, 90 and 120 minutes after administration of 0.1U/kg insulin were analyzed using repeated measures ANOVA. Differences were considered significant at $P < 0.05$.

Results

A total of 168 children were subjected to the ITT. Four of them were abandoned as they could not achieve hypoglycaemia despite repeating the dose of insulin. In 26 (15.8%) children the dose of insulin had to be repeated. Results were analyzed on 164 children, five (3%) of them had blood sugar level of <45 at baseline and they were not given insulin. Blood glucose and GH levels in these children were monitored at regular intervals without insulin administration. In the remaining 159 children, blood glucose and GH levels were monitored every 30 minutes after insulin injection.

Mean age of the subjects was 10 ± 3.5 years. There were 96 (58%) males and 68(41%) females. Overall 131 (79.8%) children developed hypoglycaemia (<45 mg/dl). Maximum number of children (35%) developed hypoglycaemia at 30 min and the percentage of children developing hypoglycaemia decreased in subsequent readings at 60, 90 and 120 minutes (Table). Seven (4.2%) children

Table: Frequency of Hypoglycaemia during ITT.

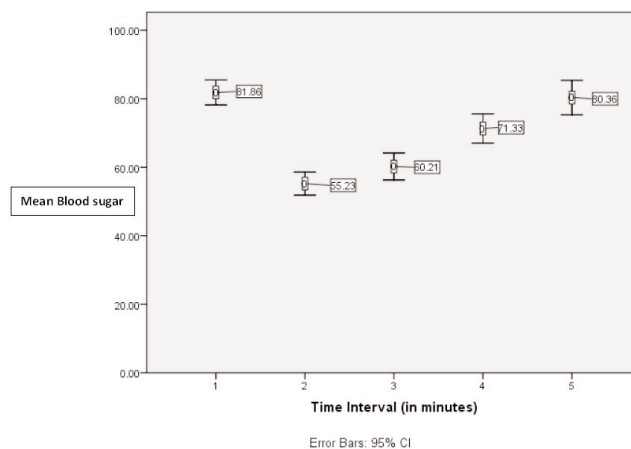| Blood glucose timings	No of children with blood sugar less than 45mg/dl.
BG1 (0 min)	5 (3%)
BG2 (30 min)	58 (35.3%)
BG3 (60 min)	35 (21.3%)
BG4 (90 min)	20 (12.1%)
BG5 (120 min)	13 (7.9%)
Total	131(79 .8%)

BG: blood glucose.

Figure-1: Mean blood sugar levels (with 95% CI) after administration of insulin.

developed clinical hypoglycaemia and had sweating and malaise although their blood glucose reading on glucometer was above 45mg/dL.

Children were closely monitored for complications. None developed significant complications of hypoglycaemia such as seizures, loss of consciousness/drowsiness or hypothermia <35ºC and the test was completed in all subjects with close monitoring. None of the children required intravenous glucose after developing hypoglycaemia or had tremors/tachycardia during the test. The test was successfully completed in all children with no serious side effect and after 4 hours of observation they were sent home.

Using repeated measures ANOVA, for the growth hormone levels and blood sugar, showed that there was a significant effect of time after insulin administration on both the blood glucose and growth hormone levels. There was a significant difference between blood glucose at baseline and the subsequent three values of blood glucose (BG) at 30, 60 and 90 minutes (BG2, BG3 and BG4) recorded. There was no significant difference between baseline blood glucose and BG 5 (at 120 min) (Figure-1). The blood glucose level decreased rapidly after administration of insulin and was lowest 30 minutes after injection and showed an increasing trend in subsequent
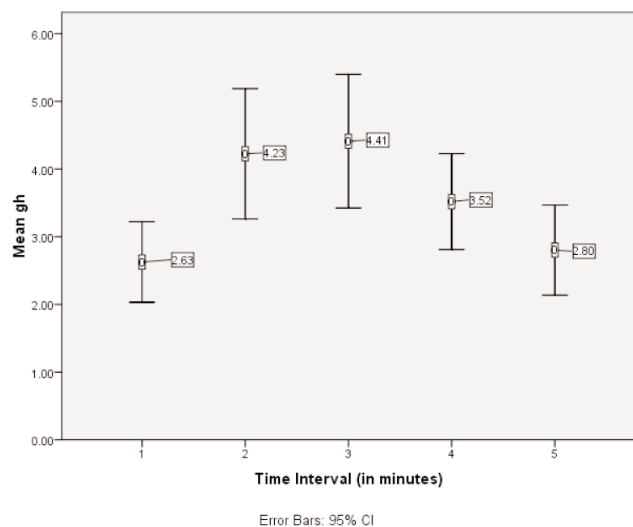
Figure-2: Mean growth hormone levels (with 95% CI) after administration of insulin.

readings, becoming equal to the baseline value 120 min after injection. The values of growth hormone were maximum 30 and 60 min after administration of insulin, coinciding with the peak of hypoglycaemia. The value of growth hormone almost reached its baseline value 120 minutes after insulin injection (Figure-2).

In the study group of 164 children, 111 (66%) were diagnosed as having growth hormone deficiency, 52 (31.3%) were normal and 1(0.6%) had growth hormone insensitivity with raised GH levels.

Discussion

The insulin tolerance test is a very specialized test which can only be performed in centers with trained personal and fully equipped to deal with any untoward incident. In our country arginine and clonidine are not available for diagnosing growth hormone deficiency and L Dopa is not commonly performed; ITT is an important and valuable test for diagnosing growth hormone deficiency but is not frequently performed and very few centers are performing it currently. Studies have shown ITT to have good diagnostic yield when compared with other studies but can lead to complications if not performed by trained staff. Our study has also shown it to have good diagnostic value as almost all children achieved hypoglycaemia and no side effects were encountered.

Growth hormone is a prolonged and quite expensive treatment with the distress of a daily injection; therefore definitive diagnosis of growth hormone deficiency is very important.[10] Studies regarding safety or documenting any adverse effects of the ITT are limited in children; but a better precision of ITT for diagnosing growth hormone

deficiency has been reported. It is still being used as a definitive test in many centers over the world but some centers perform at least two different tests before confirming growth hormone deficiency. In this study we tried to document carefully any serious complications occurring during the test due to low blood glucose and except sweating and hunger none of the children experienced any other symptoms. Side effects with ITT are very rare, not even documented in the elderly also. There had been some reports related to fatalities of ITT but this was due to high concentrations of glucose given to correct glucose.[11] However, inducing hypoglycaemia with intravenous insulin must always be seen as potentially dangerous and so very cautious patient selection by excluding those with seizure disorders or those with significant cardiac disease is mandatory.[12,13]

Very limited studies regarding the safety of ITT are available and fortunately in our study, no complications were observed. A similar conclusion has also been made by Galloway who reviewed his data of ITT in a large sample of 550 children over a ten year period and documented no serious adverse effects.[5]

A recent local study reviewing cost effectiveness of the samples of growth hormone during the ITT reported a cost effectiveness of 29 % if the 120 minute sample was not considered and they concluded that the 0 till 90 minute samples were sufficient to diagnose GH deficiency.[9] In our study group we found that almost 8% children achieved hypoglycaemia at 120 minutes and they would have been missed had the 120 minute sample been abandoned. Probably larger studies from different centers on this aspect would help to prove this and reach to a conclusion as it is very difficult to subject a child to ITT and then also not reach a definitive diagnosis.

ITT is therefore a safe test if performed in a center fully equipped and with experienced staff.

Conclusion

ITT was found to be a safe and reliable test if performed appropriately following a standard protocol with strict monitoring for side effects. It needs to be conducted in a center with expertise, staff and equipment to treat any serious problem encountered.

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