Safety of the insulin tolerance test

P J Galloway, E McNeill, W F Paterson, M D C Donaldson

Concerns have been raised about the hazards of the insulin tolerance test (ITT), used to measure growth hormone secretion. In Glasgow, we continue to use this test, adhering to a strict protocol. A review of outcome over a 10 year period (1989–99), during which 550 ITTs were performed, was undertaken. No serious adverse events occurred; in particular, no child fitted or required intravenous glucose. Fewer tests were done during the latter five years, with a higher yield of growth hormone (GH) deficiency, reflecting our increasingly conservative approach to paediatric GH therapy during this period. We conclude that the ITT is safe and reliable in a paediatric setting provided that a strict procedure is followed.

In 1991, following several fatalities in the UK, the Department of Health issued a circular warning of the hazards of the insulin tolerance test (ITT), stating that: “the insulin tolerance test should not be used in children when only growth hormone reserve needs to be tested”.

Since then many paediatric centres have abandoned the ITT as a means of assessing growth hormone (GH) reserve although it remains the standard diagnostic test for GH deficiency in adults, in view of its sensitivity and reproducibility. We have continued to use the ITT as our first line test, reserving the arginine test for children with epilepsy or cardiac disease and those under 5 years.

We have reviewed retrospectively our experience of performing ITTs over a 10 year period (1989–99), with particular attention paid to the last five years, during which a dedicated nurse specialist has been overseeing the tests. Our principal aim was to assess the safety of the ITT, defining the key morbidity measures as: (a) hypoglycaemia requiring emergency administration of intravenous glucose; (b) hypoglycaemic convulsions; and (c) death. We have also examined the timing of the glucose nadir following insulin administration as this has practical implications for oral glucose administration. Finally, in the light of a change in the pattern of GH prescribing in Scotland over the past 10 years, we have noted the annual number of ITTs performed.

METHODS

The following strict ITT protocol was adhered to:

- Child must be fasted overnight.
- Blood glucose must be >3.0 mmol/l at time −30 minutes and 0 minutes.
- Oxygen, glucose, and hydrocortisone must be available.
- A doctor must be present for 45 minutes following insulin administration and a nurse specialist throughout. (Protocol since 1995, when an endocrine nurse specialist was appointed. During the first five years of the study period, endocrine tests were carried out on a paediatric inpatient ward by junior medical staff.)
- Child must eat and remain on ward for one hour before cannula removal and discharge home.
- Administration of insulin. An insulin concentration of 1 unit/ml is used and a dose of 0.15 units/kg is given (0.1 units/kg if panhypopituitarism is suspected). The doctor must sign for the insulin and the nurse must check the dosage.
- Blood sampling. Glucose and growth hormone concentrations are measured in 4 ml samples drawn at −30, 0, 15, 30, 60, 90, and 120 minutes. The rationale of the −30 minute sample is to capture any stress related GH surge, as this may be followed by a refractory period, giving the misleading interpretation of GH deficiency.
- Management of hypoglycaemia. If the blood glucose drops below 2.2 mmol/l and/or the child is symptomatic, 30–40 ml of 50% dextrose is given intravenously, and blood glucose rechecked. Thereafter 50–100 mg hydrocortisone, followed by a 10% dextrose infusion at 0.1 ml/kg/min is given. A further dextrose bolus is administered only if blood glucose remains <6.0 mmol/l.

Statistical analysis

The relative risk of a future adverse event occurring as a result of the procedure, assuming that none had occurred to date, was calculated according to a simple formula, first described by Hanley in 1983, which states that:

\[ \text{risk} = \frac{1}{n} \]

where n = number in series (i.e. number of past, uneventful procedures).

Abbreviations: GH, growth hormone; ITT, insulin tolerance test
RESULTS
A total of 550 ITTs were performed between 1989 and 1999. No serious adverse events occurred. In particular, no child lost consciousness, fainted, or required intravenous glucose follow-
ing hypoglycaemia. The upper limit of the confidence interval for relative risk from the procedure is therefore $3/550 = 0.005 = 0.5\%$. Glucose profiles were documented for the 223 ITTs performed since 1995. The glucose nadir occurred at 15 minutes in 118 (53%) cases (range 0.6–2.2 mmol/l) and at 30 minutes in 105 (47%) cases (range 1.1–2.3 mmol/l). Between 1989 and 1992 the annual number of ITTs performed ranged from 57 to 77. During this period GH values of 10–20 mU/l were recorded in 27%. From 1993 to 1999, the annual number of ITTs performed decreased to 37–52 and the number of cases with GH values of 10–20 mU/l rose to 43%. Over the 10 year period GH values <10 mU/l were recorded in 14%. GH concentrations were >20 mU/l at time >30 minutes in 16%, indicating a normal GH response to stress, thus precluding GH deficiency.

DISCUSSION
In this assessment of the safety of the ITT in childhood we report no serious adverse events in the 550 cases studied. We acknowledge that this finding cannot preclude adverse events occurring in future patients but the probability, based on the numbers of patients studied, is, at most, 5 per thousand. Indeed no test that alters glucose homeostasis can be regarded as safe. Even the simple act of fasting a severely malnourished child may cause symptoms of hypoglycaemia. However, our experience indicates that the ITT is relatively safe provided that this endocrine investigation is carried out in a

organized manner. In this study one serious adverse event (a grand mal fit) occurred, but the patient recovered rapidly with no neurological sequelae following administration of intravenous dextrose and hydrocortisone.

It was not possible, in a retrospective study of this nature, to evaluate the degree of distress which may have been caused by the process of venepuncture, and by symptoms of insulin induced hypoglycaemia such as drowsiness, sweats, and malaise. Nor was it our remit to compare the symptoms of insulin induced hypoglycaemia with those caused by other pharmacological tests of GH secretion, such as clonidine (for example, drowsiness, hypotension), 9–11 or glucagon (for example, nausea, headache, sweating, vomiting). 12

During the 10 year study period an endocrine specialist nurse was appointed (1995) and a ward dedicated for day case investigation of children was established (1997). While it would be difficult to measure objectively an improvement in service resulting from these changes, we have no doubt that the standard of day care is much improved. Moreover, in the light of the recent changes to the working practice of junior medical staff, we consider that our endocrine day case service would be untenable without the consistent input from a specialist nurse.

The glucose nadir occurred at 15 minutes in just over half of our patients and by 30 minutes in virtually all. This finding has led us to favour the pre-emptive use of Lucozade (a readily assimilated food) rather than pharmacological agents. Moreover, insulin is easily administered and the resultant hypoglycaemia is readily reversible. The elective use of Lucozade ameliorates the symptoms of hypoglycaemia without affecting the counter regulatory response.

Other methods of GH stimulation are not without their drawbacks. While arginine administration does not result in hypoglycaemia—the increase in insulin release is balanced by a concomitant increase in glucagon, resulting in a net rise in plasma glucose— we have encountered problems with venous occlusion caused by the viscosity of the infusion, sometimes necessitating replacement of the intravenous cannula. We have no experience of other agents, but it is well recognised that clonidine causes unpleasant symptoms such as drowsiness and hypotension which are not rapidly reversible. 13 In addition, clonidine has recently been shown to be associated with hypoglycaemia, although the mechanism of action is unclear. 14 Glucagon administration causes nausea and vomiting, 12 and may also result in hypoglycaemia by stimulating insulin release. 15

Our observation that no child required intravenous dextrose in the treatment of hypoglycaemia emphasises that in virtually all cases oral glucose administration is all that is required. Indeed, fatalities associated with the ITT have involved the administration of large quantities of intravenous glucose. There is no placebo for hypoglycaemia, and no way of stimulating insulin release in children who are unable or unwilling to take food or intravenous glucose. Moreover, in children unable to respond to oral glucose, the IV route is hazardous. In neonates hypoglycaemia is readily reversible. The elective use of Lucozade ameliorates the symptoms of hypoglycaemia without affecting the counter regulatory response.

In highlighting the favourable safety record of the ITT in our hospital we are not advocating the widespread reintroduction of this method of anterior pituitary function testing, especially in departments where relatively small numbers of children are involved. Indeed, given the controversies surrounding the selection of children for investigation and treatment of GH deficiency, 16–18 we believe that the decision to embark on growth hormone stimulation testing should only be made by paediatricians who are experienced in paediatric endocrinology, and/or working in close collaboration with a regional centre.

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REFERENCES
Hospital management of asthma

I thought it would be easy: basic guidelines for hospital management of asthma. How wrong I was.

Constructing clinical guidelines is one of the tasks I’ve taken on for my year in Oshakati Hospital as a RCPCH/VSO paediatric fellow. Not wanting to be just another plastic bottle so that the cartridge can be pressed directly into a small hundred unusable inhaler refills. Not to be defeated I modified my stock I considered it my duty to drink as much fizzy pop as was needed to keep the department in steady supply of plastic bottle spacers. It didn’t take too long before I was stumped again; the inhalers were just as effective in a “breath freshener” fashion than with the silly bottle thing.

I set out to encourage the use of standardised regular doses of nebulised salbutamol with regular adrenaline. Metered dose inhalers are occasionally used for maintenance therapy when stocks of oral salbutamol run out but inhaled steroids are not used or even available (despite being on the Essential Drug List). Preventative therapy relies on theophylline and long courses of daily prednisolone.

I set out to encourage the use of standardised regular doses of nebulised salbutamol in preference to adrenaline for acute attacks. However, a Medline search I demonstrated to my colleagues to find空气中 any trial and intervention: Is this relevant for my target population? By this time my efforts have yielded little reward; most parents patiently wait, then puzzlingly ask if they can now have some proper medicine and leave without their plastic bottle. A paediatric nurse mother demonstrated to me that her child’s inhaler worked much better when I trained children have dutifully inhaled “fudha, fudha!” (breathe, breathe!).

To date, my efforts have yielded little reward; most parents patiently watch, then puzzlingly ask if they can now have some proper medicine and leave without their plastic bottle. A paediatric nurse mother demonstrated to me that her child’s inhaler worked much better when used in a “breath freshener” fashion than with the silly bottle thing.

I’m starting to comprehend the questions that must be asked of every trial and intervention: Is this relevant to my target population? And is this acceptable by my target population?

I’m prescribing oral salbutamol occasionally, the patients are happier and the clinic sister is satisfied that my consultation times are happier and the clinic sister is satisfied that my consultation times are approaching those of my colleagues (3 to 5 minutes maximum). Theophylline remains the mainstay of background control but at least prednisolone courses are shorter. I still battle on with my inhalers and spacers and they’ve even let me include them in the new guidelines.

Maybe not as many children are leaving with spacers as I’d like, but at least now that I’m drinking less fizzy pop my teeth stand a chance.

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Arch Dis Child 2002 87: 354-356
doi: 10.1136/adc.87.4.354

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