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Risk for severe hypoglycaemia with unawareness in GH deficient patients during insulin tolerance test

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Abstract

OBJECTIVE: The insulin tolerance test (ITT) is suggested as the gold standard for diagnosing GH deficiency (GHD). The ITT is, however, potentially hazardous. Glucose monitoring during the ITT varies between centres and there is surprisingly little information on the actual level of blood glucose nadir and the duration of hypoglycaemia in patients undergoing the ITT. The aim of the present study was to closely monitor the blood glucose level and to register the presence of symptoms and signs of hypoglycaemia during the ITT.

DESIGN AND PATIENTS: Sixteen patients (7 women), aged 22-59 years were consecutively recruited for an ITT, and showed GHD (peak GH < 3 µg/l).

RESULTS: In five (31%) of the patients unawareness of hypoglycaemia was recorded and the median nadir blood glucose level was 1.4 mmol/l (range 1.1-1.9) and the duration of blood glucose < 2.2 mmol/l was 25 min (range 20-33). The remaining 11 patients were symptomatic, and tiredness (n=6), and dizziness (n=3) were the most frequent symptoms. In these symptomatic patients the median nadir blood glucose level was 1.3 mmol/l (range 1.0-1.6) and the duration of blood glucose < 2.2 mmol/l was 25 min (range 15-30).

CONCLUSIONS: In patients with GHD subjected to ITT, symptoms of hypoglycaemia were scarce and a third of them showed unawareness.

Close blood glucose monitoring is recommended at ITT as low nadir blood glucose levels and long duration of hypoglycaemia may be present irrespective of symptoms of hypoglycaemia. Recommendations for intervention with intravenous glucose, at unacceptable low blood glucose levels or at prolonged hypoglycaemia, are highly warranted.

Introduction

The Growth Hormone Society has recommended the insulin tolerance test (ITT) as the diagnostic test of choice for adult GH deficiency (GHD) (GRS 1998). Alternative tests, as the GHRH-Arginine test has been recommended, (GRS 1998), but this test has limitations in e.g. patients treated with irradiation (Darzy *et al.*, 2003). The ITT is, however, potentially hazardous. In adults, unconsciousness and seizures have been reported (Jones *et al.* 1994, Lisett & Shalet 2001) and in children, mismanagement of hypoglycaemia during ITT resulted in very tragic consequences (Shah *et al.*, 1992). Glucose monitoring protocols vary between centres, and blood glucose is often only monitored at 15 or 30 min intervals (Hoffman *et al.*, 1994, Jones *et al.*, 1994). There is surprisingly little information on the actual level of blood glucose nadir and the duration of hypoglycaemia in patients undergoing ITT. Some centres give intravenous glucose or fructose to increase blood glucose at prolonged hypoglycaemia (Biller *et al.*, 2002, Lange *et al.*, 2002), but there is no uniform approach. ITT is contraindicated in patients with electrocardiographic evidence or history of ischemic heart disease or in patients with seizure disorders (GRS 1998). Given these precautions, the ITT is suggested to be safe when performed in experienced units.

It is now well established that patients with hypopituitarism on conventional hormone treatment but unsubstituted GHD have an increased prevalence of cardiovascular risk factors (Bülow *et al.*, 2000, Maison *et al.*, 2004) and an increased vascular mortality (Rosén & Bengtsson 1990, Bülow *et al.*, 1997, Tomlinson *et al.*, 2001) In addition, many patients with GHD often have a history of cranial operation and/or irradiation which gives an increased risk for seizure disorders (Constine *et al.*, 1993). Thus, in a fraction of subjects with suspected GHD the ITT must be considered as potentially hazardous, even if contraindications have not yet manifested themselves.

Another problem with the ITT is that some patients have impaired counter regulatory hormone responses to acute hypoglycaemia, involving not only GH and ACTH but, also catecholamine responses, which has been shown in children with both isolated and multiple pituitary hormone deficiencies (Vorhess *et al.*, 1984, Chalew *et al.*, 1986).

The procedure of the ITT has been described in detail (Ho 2001), i.e. adequate hypoglycaemia occurs when the blood glucose level falls to < 2.2 mmol/l associated with symptoms of neuroglycopenia, including tachycardia and sweating. However, when performing numerous ITTs in GHD patients we had the impression that symptoms of hypoglycaemia

were scarce and sometimes even absent. Further, the blood glucose level was often very low, and the recovery slow.

The main aim of the present study was to closely monitor the blood glucose level and to register the presence of symptoms of hypoglycaemia during the ITT, in a group of consecutively recruited patients with a high suspicion of GHD.

Patients and Methods

Sixteen patients (7 women) were consecutively recruited for the ITT due to a high probability of GHD (Table 1). Patients with a history of cardiovascular disease, seizure disorders or ≥ 60 years of age were not included. The median age was 39 years (range 22-59) and their body mass index (BMI) was 25.5 kg/m^2 (range 20.0-33.7). Detailed information on background diagnosis and pituitary deficiencies is given in Table 1.

The patients arrived at 7.30 AM and were fasting since midnight. Twelve of 16 patients were hormonally substituted for pituitary insufficiencies. After intake of their morning medication including also cortisone, intravenous cannulas were inserted into the left and right forearm veins and were kept patent by short regular flushes of saline. A nurse and a physician were present during the whole ITT.

In our Endocrine unit the ITT is a 90-min test and serum GH is analyzed at -15, 0, 15, 30, 45, 60, 75 and 90 min. At 0 min insulin (Actrapid; Novo Nordisk, Gentofte, Denmark) is administered as an intravenous bolus of 0.1 IU/kg. The dose was often reduced by 10-40 %, if concomitant pituitary deficiency, especially ACTH deficiency, was present (Table 1). Blood glucose was analyzed from the forearm vein and monitored at -15, 0, 10, 15, 20, 25, 30, 35 min and then every 5 to 10 min up to 90 min. At a blood glucose level around 2.2 mmol/l more frequent (every other minute) blood glucose testing was performed. During this period the patients were interviewed with respect to symptoms of body heat, dizziness, tiredness, palpitations, and blurred vision. Furthermore, their pulse, tendency of sweating and paleness was registered during the hypoglycaemic phase. When the blood glucose level was below 2.0 mmol/l oral fructose or juice was given, and at blood glucose levels around 1.3 mmol/l or if the hypoglycaemia was prolonged (≥ 25 min) an intravenous bolus infusion of glucose (30%) was administered (Table 1). In nine patients (2 patients with unawareness) who had prolonged hypoglycaemia intravenous glucose (30%) as a bolus infusion was given.

Venous blood glucose was analysed with Hemocue Blood Glucose Analyser (Hemocue AB, Ängelholm, Sweden). According to the

manufacturer, the standard deviation between the cuvettes is < 0.3 mmol/L. Serum GH was analysed by an immunofluorometric method, DELFIA hGH (Wallac Oy, Turku, Finland). The detection level for serum GH was $0.01 \mu\text{g/L}$ and at a level of $1.5 \mu\text{g/l}$ the intra- and interassay CV was 5 % and 3 %, respectively, and at a level of $7.7 \mu\text{g/l}$ the intra- and interassay CV was 3 % and 5 %, respectively. The recommendations for cut-off values for the ITT are based on the results obtained with polyclonal competitive RIAs calibrated against the pituitary derived preparation International Reference Preparation (IRP) 80/505 ($1 \text{ mg} = 2.6 \mu\text{g/l}$) (1).

Results

All patients were GHD confirmed by a peak GH $< 3 \mu\text{g/l}$ to the ITT (Table 1). The median insulin dose used was 0.07 IU/kg (range $0.06\text{-}0.1$). The median nadir blood glucose level for the whole group was 1.3 mmol/l (range $1.0\text{-}1.9$) and was reached at a median 25 min (range $20\text{-}33$) after the insulin infusion. The median duration of hypoglycaemia (blood glucose $< 2.2 \text{ mmol/l}$) was for the whole group 25 min (range $15\text{-}33$). All symptoms recorded during the ITT are shown in Table 1.

In five (31%) of the patients neither the physician nor the patient recorded any signs or symptoms during the hypoglycaemic phase and their median nadir blood glucose level was 1.4 mmol/l (range $1.1\text{-}1.9$) and the duration of blood glucose $< 2.2 \text{ mmol/l}$ was 25 min (range $20\text{-}33$). Of these five

patients with unawareness, four had panhypopituitarism and one had isolated GHD. The remaining 11 patients were symptomatic, and tiredness (n=6), and dizziness (n=3) were the most frequent symptoms. In these patients with symptoms, the median nadir blood glucose level was 1.3 mmol/l (range 1.0-1.6) and the duration of blood glucose < 2.2 mmol/l was 25 min (range 15-30) (Table 1). No clear difference in the nadir blood glucose level (blood glucose 1.25 mmol/l and 1.35 mmol/l, respectively), or in the duration of hypoglycaemia (25 min, respectively) was recorded among the eight patients with or without ACTH insufficiency.

Discussion

In five (31 %) of 16 consecutively recruited patients investigated with an ITT because of a high probability of GHD, hypoglycaemia with unawareness was recorded, and in the rest of the patients symptoms of hypoglycaemia were scarce, compared to what has been recorded in normal subjects (Mitrakou *et al.*, 1991). Further, similarly low nadir blood glucose levels were recorded during the ITT for both those with symptoms and those with unawareness. Unawareness seems to be a new finding in this patient group, and we can only find one report in the literature, by Merimee *et al.* (1971), who also noted a “remarkable lack of hypoglycaemic symptoms” in GHD dwarfs during ITT. The phenomenon is, however, well known among patients with diabetes mellitus and seems

to be due to an adaptation to a long duration of diabetes and to frequent hypoglycaemic attacks (Gerich *et al.*, 1991). Of interest, is a previous report showing that GH treatment for a week restored hypoglycaemia awareness in four patients with insulin-treated diabetes (Wurzburger *et al.*, 1992). However, improvement of awareness or counter regulatory hormone response could not be reproduced in another study, with seven days of GH treatment to insulin-dependent diabetic patients (Sachon *et al.*, 1993). In addition, previously we reported that counter regulatory hormones (plasma catecholamines, serum glucagon and cortisol), were unchanged during a hypoglycaemic glucose clamp in GHD subjects before compared to after nine months of GH treatment (Bülow *et al.*, 1999). However, hypoglycaemic symptoms and awareness were unfortunately not registered. Thus, if restoration of unawareness or of counter regulatory hormone responses is possible with GH treatment remains to be further elucidated. However, it has to be pointed out that s.c daily injections of GH is hardly comparable to a physiological hypoglycaemic GH response.

No control group was provided in the present study, but there is plenty of information in the literature suggesting that the glycaemic threshold for activation of counter regulatory systems in normal subjects had been reached in all patients. When using the stepped hypoglycaemic glucose clamp technique in normal subjects, the arterialized venous glycaemic

threshold for increments in glucagon, epinephrine and GH was 3.8 mmol/l (Mitrakou *et al.*, 1991). Further, in normal subjects hypoglycaemia induces autonomic functions, e.g. anxiety, palpitations, sweating which begins at a blood glucose level of 3.2 mmol/l (Mitrakou *et al.*, 1991). Furthermore, neuroglycaemic symptoms, i.e. hunger, tingling, blurred vision, difficulty in thinking, faintness, begin at a blood glucose level of 2.8 mmol/l (Mitrakou *et al.*, 1991). Thus, in comparison to normal subjects it seems quite obvious that the commonly reported symptoms during an ITT were scarce or even missing in the present study population. The most frequent symptoms in the present study were tiredness and dizziness (Table 1). The lack of perspiration in the majority of patients is probably explained by GHD *per se* (Pedersen *et al.*, 1989). Biller *et al.* (2002), reported a somewhat higher percentage of subjects with both hypoglycaemia and hypoglycaemic symptoms (79 % reported sweating) in patients undergoing ITT. In this report (Biller *et al.*, 2002), the patients were much more obese in comparison to the present study, which perhaps may be of importance.

A reduction of the insulin dose during the ITT has been recommended in children when additional pituitary hormone insufficiency is present (Shah *et al.*, 1992, Sizonenko *et al.*, 2001), but to our knowledge there is no such recommendation in adults. In spite of a reduction of the insulin dose (0.07

IU/kg) in the present study, which was lower than the currently recommended standard dose of insulin (0.15 IU/kg body weight) (Loriaux & McDonald 2001), very low nadir blood glucose levels were recorded. No clear difference in the nadir blood glucose level was recorded among the eight patients with or without ACTH insufficiency, which would speak in favour of GH as a major counter regulatory hormone. One explanation for the very low blood glucose levels recorded during the ITT in the present study could be the close monitoring of blood glucose around the expected nadir. This procedure was in contrast to other studies where glucose monitoring at 15 min or 30 min intervals had been practiced (Hoffman *et al.*, 1994, Jones *et al.*, 1994). Thus, a short-term very low blood glucose level during an ITT can thus be missed.

There was a long duration of hypoglycaemia in the present study and no difference between the groups with and without unawareness. This is in contrast to normal subjects, where an injection of 0.15 U/kg iv will result in a burst of glucose production from accelerated glycogenolysis, causing a rapid correction of hypoglycaemia (Garber *et al.*, 1976). Thus, the nadir of plasma glucose will only last about 5 min, at a mean plasma glucose level just above 2 mmol/l, and will thereafter steadily increase to normal levels (Garber *et al.*, 1976). A slow recovery from hypoglycaemia during an ITT has been shown in adults with multiple pituitary

deficiencies (Garg *et al.*, 1994) and ACTH- and GH insufficiency have been suggested as primarily responsible (Garg *et al.*, 1994). There was however, no difference in the duration of hypoglycaemia between the eight patients with or without ACTH insufficiency, which would again favour GH as more important for a quick recovery of insulin-induced hypoglycaemia.

The ITT has probably the greatest potential of all hormone tests for causing short term impairment of elementary cognitive function, which has been shown in both normal subjects and in patients with diabetes mellitus (Lobmann *et al.*, 2000). In the present study prolonged low blood glucose levels, even without signs as unconsciousness, was counteracted with intravenous bolus of glucose, which is in accordance with common practices (Biller *et al.*, 2002, Lange *et al.*, 2002). Whether blood glucose levels around 1.3 mmol/l during 25 min may cause some type of minimal brain damages is not known.

In conclusion, in 16 consecutively recruited patients subjected to the ITT which showed GHD, the overall symptoms of hypoglycaemia were scarce and in 5 (31%) unawareness was recorded. Furthermore, low nadir blood glucose levels and long durations of hypoglycaemia were recorded, irrespective of ACTH deficiency. These results further emphasize the

recommendation from the Growth Hormone Research Society that the ITT should only be performed in experienced units (GRS 1998). If the ITT is still going to be recommended as the gold standard for diagnosing GHD we ask for more uniform recommendations, e.g. dose of insulin. Furthermore, to avoid future complications during the ITT, recommendations for intervention with intravenous glucose, at unacceptable low blood glucose levels or at prolonged hypoglycaemia, are highly warranted.

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Table 1. Detailed information on 16 patients with GH deficiency (peak GH < 2.4 ug/L), investigated with an insulin tolerance test (ITT). *ALL; acute lymphoblastic leucemia.

Pt #	Gender F/M	Age yr	BMI kg/m ²	Diagnosis	Radio-therapy Yes/no	Other pituitary deficiency at investigation	Insulin IU/kg	B-glucose at -15 min mmol/l	Nadir b-glucose mmol/l	Nadir b-glucose (min from time 0)	Duration of b-glucose ≤ 2.2 mmol/l	Peak GH µg/l	Symptoms and signs of hypoglycaemia	Intra-venous glucose during the test
1	M	25	20.0	Epipharynx cancer	Yes	TSH	<0.1	4,1	1.2	30	15	0.27	Anxiety, tachycardia	No
2	M	54	24.3	Non-functioning Pituitary adenoma	Yes	Panhypo	0.09	4,4	1.4	20	20	0.15	None	No
3	F	51	28.7	Cranio-pharyngioma	Yes	Panhypo	0.08	4,8	1.3	27	27	0.27	Tired, warm	Yes
4	M	39	25.4	Idiopathic	No	Panhypo	0.07	4,9	1.1	30	30	< 0.03	None	Yes
5	F	21	22.2	Non-functioning Pituitary adenoma	No	Panhypo	0.1	4,2	1.0	30	30	<0.03	Dizzy, tired, Pale	Yes
6	F	53	28.0	Prolactinoma	Yes	Panhypo	0.07	4,5	1.5	22	22	0.12	None	No
7	M	53	23.8	Non-functioning Pituitary adenoma	Yes	FSH, LH,	0.08	4,6	1.2	25	25	0.22	Blurred vision	Yes
8	M	59	25.8	Non-functioning Pituitary adenoma	Yes	TSH, ACTH,	0.08	4,1	1.2	25	25	0.22	None	Yes
9	M	47	27.6	Empty sella	No	No	0.07	4,4	1.9	33	33	0.14	None	No
10	F	22	25.6	ALL*-irradiation therapy	Yes	No	0.07	4,7	1.2	25	25	0.81	Dizzy, pale, tired, perspiring	Yes
11	M	25	25.7	ALL-irradiation therapy	Yes	No	0.08	4,1	1.6	25	25	2.4	Dizzy, pale, tired, perspiring	No
12	M	22	20.1	Idiopathic	No	No	0.07	4,2	1.5	25	25	0.58	Perspiring, warm	No
13	F	39	28.2	Non-functioning Pituitary adenoma	No	TSH	0.06	4,4	1.3	25	25	0.22	Shaky	Yes
14	F	30	33.7	Non-functioning Pituitary adenoma	Yes	TSH, FSH, LH	0.07	4,6	1.4	30	30	0.05	Warm	No
15	M	45	24.7	Non-functioning Pituitary adenoma	No	Panhypo	0.06	4,0	1.3	25	25	0.42	Warm, tired	Yes
16	F	51	24.0	Acromegaly (cured)	Yes	Panhypo	0.07	4,6	1.2	25	25	0.1	Tired, sleepy	Yes