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ORIGINAL ARTICLE

Factors determining inadequate hypoglycaemia during insulin tolerance testing (ITT) after pituitary surgery

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Summary

Background Some patients fail to achieve adequate hypoglycaemia following a standard dose of intravenous insulin during the insulin tolerance test (ITT). Persistent acromegaly or Cushing's disease may contribute to inadequate hypoglycaemia.

Aim To identify factors that predict failure to achieve adequate hypoglycaemia during an ITT after pituitary surgery.

Methods We reviewed consecutive ITTs performed over a 10-year period in 76 patients following pituitary surgery. Analyses were performed to determine if body mass index (BMI), fasting blood glucose (FBG), cortisol, GH status or underlying diagnosis influenced the outcome.

Results Adequate hypoglycaemia (blood glucose < 2·2 mmol/l) was not achieved in 33 patients (Group 1) following a standard dose of neutral insulin (0·1 units/kg); 43 patients (Group 2) achieved adequate hypoglycaemia. Group 1 had significantly higher BMI, FBG, baseline cortisol and peak cortisol concentrations than Group 2. Peak GH response was not different. Multiple regression analysis showed that FBG was the only independent predictor of adequate hypoglycaemia. An insulin dose of 0·2 units/kg achieved adequate hypoglycaemia in 80% of patients with FBG ≥ 5·5 mmol/l. In patients with acromegaly or Cushing's disease, failure to achieve adequate hypoglycaemia was associated with persistent disease.

Conclusion FBG is an important determinant of the dose of insulin required to achieve adequate hypoglycaemia during an ITT in patients after pituitary surgery. A standard insulin dose of 0·1 U/kg is insufficient for adequate hypoglycaemia in patients with FBG > 5·5 mmol/l. Adequate response to a standard dose of insulin suggests a likelihood of cure of acromegaly or Cushing's disease after pituitary surgery.

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Introduction

The insulin tolerance test (ITT) is the gold standard test for evaluating pituitary–adrenal status after pituitary surgery.[1–3] However, some patients fail to achieve adequate hypoglycaemia after a standard dose of insulin. The reasons are likely to involve factors that impact insulin sensitivity. For such patients, a second, usually larger, dose is administered, thus prolonging a procedure with some inherent risk.

The aim of this study was to identify factors that contribute to inadequate hypoglycaemia during an ITT following pituitary surgery. We report a retrospective analysis of demographic, biochemical and endocrine factors in consecutive patients with pituitary disease who underwent an ITT over a 10-year period.

Subjects and methods

Patient population

A retrospective review was performed on 76 consecutive patients who underwent an ITT after pituitary surgery from January 1998 to August 2007. They comprised patients with non-functional tumours ($n = 37$), prolactinomas ($n = 16$), acromegaly ($n = 8$), Cushing's disease ($n = 6$), hypophysitis ($n = 3$), craniopharyngiomas ($n = 3$) and parasellar meningiomas ($n = 3$). Baseline biochemistry and patient characteristics including age, sex, underlying diagnosis and weight were recorded. No patient had a past history of diabetes mellitus.

Endocrine evaluation

The ITT was performed approximately 6 weeks after pituitary surgery. Immediately following surgery, all patients were placed on a tapering dose of glucocorticoids, reducing to a replacement dose before discharge (dexamethasone 0·25 mg/day; prednisolone 5 mg/day; hydrocortisone 20 mg/day). The ITT was conducted as described previously.[4] Briefly, patients presented to the Clinical Research Facility, Garvan Institute of Medical Research, after fasting from the previous night and omitting their morning medications, including glucocorticoids. Weight was measured with the patient in light street clothing. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in metres. A fasting blood sample was taken for measurement of baseline glucose, cortisol, T4 and pituitary hormones (GH, LH, FSH, PRL). A

standard dose of neutral insulin (Actrapid®) was administered intravenously (0·1 unit/kg). Blood glucose level was measured every 5 min by an endocrine nurse. Blood samples were taken every 30 min for 120 min for measurement of GH and cortisol after adequate hypoglycaemia was achieved. Adequate hypoglycaemia was defined as a blood glucose (BG) concentration < 2·2 mmol/l occurring in parallel with the development of hypoglycaemic symptoms.[3] A second (0·15 units/kg) or third (0·2 units/kg) dose of insulin was administered when a nadir glucose level < 2·2 mmol/l was not reached and at least two consecutive values showed an upward trend. Remission of acromegaly was defined as reduction of IGF-1 into the normal range (< 1·6 U/ml). Remission of Cushing's disease was defined as normalization of urinary free cortisol (UFC) excretion (< 300 nmol/24 h).

Laboratory techniques

BG was measured using the glucose oxidase method on venous blood (model 23AM; Yellow Springs Instrument Co., Yellow Springs, OH). Serum cortisol was analysed using the ADVIA Centaur® Immunoassay System, and GH was measured by ELISA, as previously described.[5] The ELISA has a sensitivity of 0·001 μg/l, intra-assay coefficients of variation (CV) of 6% and 8% ($n = 14$), and inter-assay CV of 10% and 9% ($n = 10$) at 0·08 and 2 μg/l GH, respectively. IGF-I was measured by RIA after acid–ethanol extraction[6] with an intra-assay CV 6·1%.

Statistical analysis

Results are shown as mean ± SD for normally-distributed variables and geometric mean (interquartile range) for skewed data (GH). The latter was log-transformed in statistical analysis. Differences between those subjects achieving adequate hypoglycaemia *vs.* those who did not, were analysed by the unpaired *t*-test. Differences between categorical variables were assessed using the χ^2-test. Backward stepwise multiple regression was performed to determine independent predictors of adequate hypoglycaemia. $P < 0·05$ was considered statistically significant.

Results

Thirty-three patients (Group 1: age 45·2 ± 4·5 year, 14 women) failed to achieve adequate hypoglycaemia after a standard dose of intravenous insulin, while 43 patients (Group 2: age 47·7 ± 5·7 year, 22 women) did. Patients in Group 1 were given a second dose of insulin 45 min after the first injection, 50–100% higher than the original dose. Twenty-eight patients achieved adequate hypoglycaemia following a second dose of insulin (0·1–0·2 units/kg). Four patients required a third dose at 0·3 units/kg. One ITT was terminated, as the patient did not achieve adequate hypoglycaemia with a cumulative dose of 1 unit/kg of insulin. The patient subsequently proved to have persistent Cushing's disease.

Compared to Group 2, patients in Group 1 had significantly higher body weight (89·3 ± 18·9 *vs.* 79·1 ± 19·0 kg, $P = 0·02$), BMI (30·8 ± 5·0 *vs.* 26·5 ± 6·4 kg/m^2, $P = 0·002$), fasting BG (FBG) concentration (5·4 ± 0·7 *vs.* 4·5 ± 0·40 mmol/l, $P < 0·0001$), baseline cortisol concentration (297 ± 118 *vs.* 215 ± 117 nmol/l, $P = 0·003$) and peak cortisol concentration (543 ± 299 *vs.* 383 ± 197 nmol/l, $P = 0·006$). Patients who achieved adequate hypoglycaemia were more likely to be adrenal insufficient (peak cortisol < 500 mmol/l) compared to those who failed to achieve adequate hypoglycaemia (65% *vs.* 42%, $P < 0·01$). There was no difference between the groups in peak GH response [9·1 (0·4–40·9) mU/l *vs.* 9·9 (0·4–76·5) mU/l]. GH deficiency (peak GH < 15 mIU/l) was not associated with increased susceptibility to hypoglycaemia.

Examination of the range of FBG levels revealed that all values from Group 2 were < 5·5 mmol/l, whereas 45% of values from Group 1 were over this threshold ($P < 0·001$; Fig. 1: left panel). In this subgroup of patients with FBG > 5·5 mmol/l, there was a significant positive correlation between FBG and the cumulative dose of insulin required to achieve hypoglycaemia ($r = 0·88$, $P = 0·04$; Fig. 2: left panel). There was also a significant correlation between FBG and the final dose that achieved adequate hypoglycaemia ($r = 0·72$, $P = 0·02$; Fig. 2: right panel).

As persistence of acromegaly and Cushing's disease is associated with insulin resistance, the data were reanalysed after excluding patients with acromegaly and Cushing's disease ($n = 14$). The findings were similar, with Group 1 patients having significantly higher weight, BMI, FBG level and baseline and peak cortisol concentrations compared to Group 2 patients (data not shown). The mean peak GH response was not statistically different (data not shown). Backward step-wise multiple regression was performed to determine the contribution of BMI, FBG, baseline and peak cortisol and GH concentrations to inability to achieve adequate hypoglycaemia during an ITT. In this model, only FBG independently predicted adequate hypoglycaemia during ITT (adjusted $R^2 = 0·4$, $P < 0·0001$).

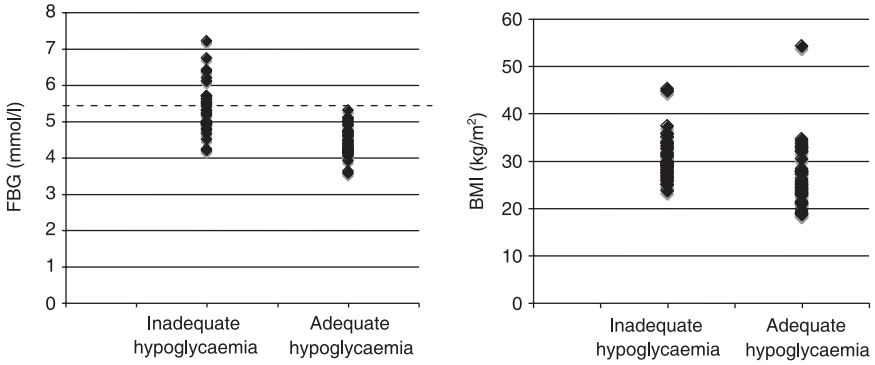

Fig. 1 Distribution of fasting blood glucose (FBG) concentration (left panel) and BMI (right panel) in patients who achieved adequate hypoglycaemia and in those who failed to achieve adequate hypoglycaemia. Fasting blood glucose concentration (FBG) was < 5·5 mmol/l in all the patients who achieved adequate hypoglycaemia.

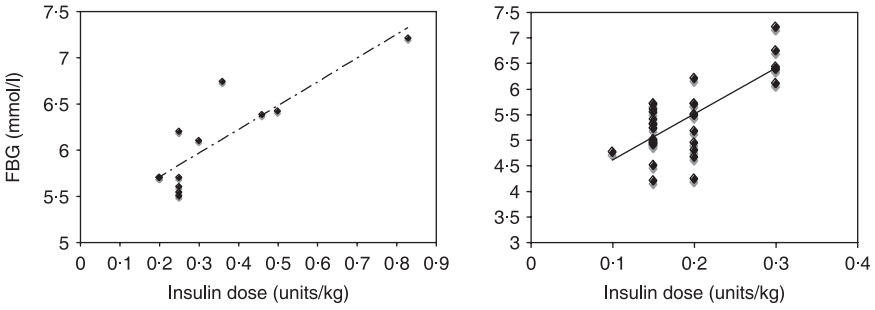

Fig. 2 Relationship between fasting blood glucose (FBG) and cumulative insulin dose (left panel: $r = 0{\cdot}88$, $P = 0{\cdot}04$) and final insulin dose (right panel: $r = 0{\cdot}72$, $P = 0{\cdot}02$).

Among patients with acromegaly and Cushing's disease ($n = 14$), a greater proportion of patients with persistent disease (acromegaly: 6, Cushing's disease: 1) failed to achieve adequate hypoglycaemia compared to those in remission (67% *vs.* 13%, respectively, $P = 0{\cdot}03$). Weight ($91{\cdot}9 \pm 15{\cdot}5$ kg *vs.* $92{\cdot}1 \pm 30{\cdot}4$ kg, $P = 0{\cdot}9$), BMI ($31{\cdot}6 \pm 4{\cdot}6$ kg/m^2 *vs.* $30{\cdot}3 \pm 11{\cdot}2$ kg/m^2, $P = 0{\cdot}7$) and FBG ($5{\cdot}32 \pm 1{\cdot}13$ mmol/l *vs.* $4{\cdot}71 \pm 0{\cdot}42$ mmol/l, $P = 0{\cdot}2$) were not different between the patients with persistent disease and those in remission.

Discussion

In this retrospective audit of 76 patients who underwent an ITT following pituitary surgery, 43% of patients failed to achieve adequate hypoglycaemia following a standard weight-based dose of intravenous insulin. BMI, FBG and baseline and peak cortisol levels were higher among those who did not achieve hypoglycaemia. However, in a multiple regression analysis, FBG level was the only significant predictor explaining 40% of the likelihood of achieving hypoglycaemia. Persistence of disease in patients with acromegaly and Cushing's disease was associated with a reduced likelihood of achieving adequate hypoglycaemia during ITT.

Our study demonstrates that factors associated with insulin resistance,[7] such as obesity and fasting hyperglycaemia, both influenced the ability to achieve adequate hypoglycaemia following insulin administration. We observed an arbitrary FBG threshold of 5·5 mmol/l, below which hypoglycaemia was attained after insulin, and above which the probability of failure to achieve hypoglycaemia was increased. The threshold of 5·5 mmol/l corresponds to that defined as impaired fasting glucose (IFG) by American Diabetes Association criteria.[8] In other words, patients with IFG were less likely to achieve adequate hypoglycaemia during ITT. Although not measured in our study, it is likely that insulin resistance, particularly hepatic insulin resistance, which is associated with impaired suppression of endogenous glucose production during a hyperinsulinaemic–euglycaemic clamp,[9,10] explains failure to achieve adequate hypoglycaemia during an ITT in patients with increased weight and higher FBG levels.

The standard dose of insulin used for the ITT is variable, ranging from 0·1 to 0·15 units/kg[11–16] Many endocrine services,[11–13] including our own, utilize a standard weight-based insulin regimen (0·1 units/kg) for the ITT, while other centres empirically use a higher dose (0·15–0·2 units/kg) for overweight or obese patients in anticipation of a greater degree of insulin resistance[3,17] or in patients with acromegaly.[18] This is in agreement with univariate analysis of our study, as patients who failed to achieve adequate hypoglycaemia were heavier. However, multiple regression analysis revealed FBG, but not weight nor BMI, as the only independent predictor of adequate hypoglycaemia, consistent with a previous audit.[13] Analysis of data distribution failed to reveal a predictive BMI threshold, in contrast to that for FBG (Fig. 1). Further analysis revealed a strong relationship between FBG and either the cumulative or the greatest dose of insulin required to achieve hypoglycaemia (Fig. 2). As the half-life of intravenous insulin is in the order of minutes, and the second dose of insulin was given at least 45 min after the first dose, the BG nadir achieved by the second dose would be very largely related to that dose. As the second dose was administered after there had been lowering of the BG, the first dose is likely to have made only a small contribution to the final nadir BG. Our observation suggests that a higher insulin dose should be considered in patients with IFG (> 5·5 mmol/l) and that the dose should be based on the degree of fasting hyperglycaemia. Our data indicate that doubling the insulin dose to 0·2 units/kg is appropriate for patients with FBG of 5·5–5·9 mmol/l and that 0·3 units/kg may be necessary for patients with FBG ≥ 6 mmol/l (Fig. 2). As hypoglycaemic failure was 100% in patients with FBG > 5·5 mmol/l, and 32% in those with FBG < 5·5 mmol/l, the dose used in our regimen of 0·1 units/kg should be reserved for patients with FBG < 5·5 mmol/l and in those suspected of having adrenal insufficiency. However, because up to two thirds of patients with FBG < 5·5 mmol/l given 0·1 units/kg of insulin achieve adequate hypoglycaemia, increasing the insulin dose without considering the FBG could increase the severity and duration of hypoglycaemia.

Baseline and peak cortisol concentrations were also predictors of inadequate hypoglycaemia during the ITT in our study. Group 2 has significantly lower baseline and peak cortisol than Group 1. Cortisol enhances hepatic glucose production[19] and the lower cortisol level observed in Group 2 may be associated with greater insulin sensitivity and achievement of adequate hypoglycaemia. Baseline cortisol level (e.g. from a preceding measurement) may be utilized as another indicator to adjust the insulin dose used for ITT.

Among patients who had pituitary surgery for acromegaly or Cushing's disease, failure to achieve adequate hypoglycaemia occurred more frequently in those with persistent disease, consistent with known antagonistic effect of GH and cortisol on insulin sensitivity. Active acromegaly induces both hepatic and peripheral insulin resistance,[20,21] while hypercortisolism in active Cushing's disease

stimulates gluconeogenesis, antagonizes insulin action and increases insulin resistance with progressive obesity.[22] Thus the ITT maybe a useful indicator of persistent acromegaly and Cushing's disease following pituitary surgery while awaiting confirmation from elevated IGF-1 concentration and UFC excretion, respectively. The dose of insulin should be increased in patients confirmed to have persistent disease before the ITT.

In conclusion, FBG is an important determinant of the dose of insulin required to achieve adequate hypoglycaemia during an ITT in patients after pituitary surgery. In those with FBG ≥ 5·5 mmol/l, a dose > 0·1 U/kg is required to obviate the need for a second dose. Failure to achieve adequate hypoglycaemia in patients who have undergone pituitary surgery for acromegaly or Cushing's disease is a likely indicator of persistent disease.

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