CLINICAL STUDY

Insulin sensitivity and glucose tolerance improve in patients with acromegaly converted from depot octreotide to pegvisomant

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Abstract

Aim and method: Insulin resistance leading, in some cases, to glucose intolerance is an important contributory factor to the cardiovascular morbidity and mortality associated with acromegaly. The aim of this study was to document changes in insulin sensitivity (IS) in a group of seven patients with acromegaly (three male, four female, mean $\pm$ S.D. age 59 ± 13 years) treated initially with a stable dose of depot octreotide (OT; median dose 30 mg four times weekly, range 10–30 mg) for a median of 18 months (range 16–19 months) and who were then transferred to treatment with pegvisomant (median dose 15 mg daily, range 10–20 mg) for a median of 8 months (range 7–9 months). IS was assessed by homeostatic model assessment (HOMA) using fasting glucose and insulin concentrations and by a short insulin tolerance test (sITT). Body composition was assessed by dual energy X-ray absorptiometry.

Results: Mean $\pm$ S.D. serum IGF-I concentrations during therapy with OT and with pegvisomant were not statistically different (283 ± 119 ng/ml on OT vs 191 ± 39 ng/ml on pegvisomant ($P = 0.4$)). However, mean $\pm$ S.D. fasting plasma glucose fell from 6.2 ± 1.0 mmol/l on OT to 5.2 ± 0.6 mmol/l on pegvisomant ($P = 0.017$) and was lower on pegvisomant in all seven patients. In four patients, fasting plasma glucose fell from values diagnostic of diabetes mellitus or impaired fasting glucose on OT to within the normal range on pegvisomant. Mean $\pm$ S.D. peripheral IS (by sITT) increased from 139 ± 39 μ mol/l per min on OT to 169 ± 59 μ mol/l per min on pegvisomant ($P = 0.037$). Mean $\pm$ S.D. IS (by HOMA %S) was unchanged over the course of the study ($149.1 \pm 43.7\%$ on OT vs $139.9 \pm 76.6\%$ on pegvisomant, $P = 0.28$). Mean $\pm$ S.D. pancreatic β -cell secretory function (HOMA %B) improved significantly on pegvisomant compared with OT ($49.4 \pm 19.2\%$ vs $82.4 \pm 43.5\%$, $P = 0.01$). No statistically significant change in total fat ($P = 0.3$), % fat ($P = 0.28$) or circulating non-esterified fatty acids ($P = 0.35$) was observed.

Conclusions: IS and glucose tolerance improved in patients converted from OT therapy to pegvisomant, without a change in body composition and even when serum IGF-I concentrations remained equally well controlled. This may be an important factor in the choice of medical therapy for patients with acromegaly.

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Introduction

It is well established that aggressive control of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis restores the excess mortality rate associated with acromegaly to that of the general population (1, 2). However, transphenoidal surgical adenomectomy establishes 'safe' GH levels in less than 50% of patients with a macroadenoma (3) and external beam pituitary irradiation, although an effective adjunctive treatment, works slowly (4, 5). Hence, many patients who are not cured by surgery or who are awaiting the effects of pituitary irradiation, require medical therapy to control the GH/IGF-I axis. Current options for medical therapy include dopamine agonists (usually cabergoline (6))

and somatostatin analogues, either in short-acting form (octreotide acetate (7)) or as intramuscular depot preparations (octreotide (8) or lanreotide (9)). The advent of the GH receptor (GHR) antagonist pegvisomant, which is able to normalise serum IGF-I concentrations in 97% of patients with active acromegaly (10–12), means that endocrine physicians will soon have several options for medical therapy available for use either alone or in combination.

The increased cardiovascular morbidity and mortality associated with acromegaly is, at least in part, consequent upon the increased insulin resistance (IR) that frequently accompanies GH hypersecretion. Somatostatin analogues achieve 'safe' GH and IGF-I concentrations in approximately 60% of patients, but

their inhibitory effect on pancreatic insulin secretion dictates that their overall effect on glucose tolerance is complex and unpredictable (13, 14). It is therefore possible that differences in the effect of somatostatin analogues and pegvisomant on insulin sensitivity (IS) and glucose tolerance may influence the choice of medical therapy for an individual patient. The aim of this study was to compare IS, using two complementary methodologies, in a group of seven patients with active acromegaly converted from stable therapy with a long-acting somatostatin analogue to treatment with pegvisomant.

Patients and methods

Patients

Details of the seven patients (three male, four female, mean $\pm$ S.D. age 59 ± 13 years) studied are given in Table 1. All had active acromegaly and were receiving appropriate replacement therapy for the pituitary hormone deficits as shown, doses of which did not change during the course of the study (Table 1).

Study protocol

The patients were participating in a multi-centre, open-label study of the efficacy of pegvisomant in the treatment of acromegaly. All were treated with a stable dose of depot octreotide (OT; median duration of treatment 18 months, range 16–19 months (Novartis Pharma AG)) and all were receiving the maximum effective dose (median 30 mg four times weekly, range 10–30 mg), judged by the mean of five serum GH concentrations taken through the day and serum IGF-I measurements. Following informed, ethical board-approved consent, the next scheduled OT injection was withheld and treatment with pegvisomant (Pharmacia Corp.) commenced, initially at a dose of 10 mg once daily by subcutaneous injection. The dose of pegvisomant was increased, if necessary, every 8 weeks, up to a maximum of 25 mg daily, in order to maintain the serum IGF-I concentration within the age-adjusted normal range.

IS was measured at baseline (on OT, within 48 h of the scheduled, withheld dose) and again after a

median of 8 months (range 7–9 months) therapy with pegvisomant and was assessed by two methods: homeostatic model assessment (HOMA) and a short insulin tolerance test (sITT). In the latter test, with the patient in the fasting state, 0.1 IU/kg body weight of soluble insulin is injected intravenously and samples drawn for plasma glucose at 0, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15 min. The rate of fall of plasma glucose (calculated using Excel, Microsoft, Seattle, WA, USA) provides a reproducible measure of peripheral IS and has been validated against the 'gold standard' hyperinsulinaemic euglycaemic clamp (15). The HOMA is a computer solved model for predicting IS (%S) and β -cell deficiency (%B) (16) and has been shown to be useful for predicting IS in acromegaly (17).

Measurements and assays

Plasma glucose was measured by the glucose oxidase method. Plasma insulin concentrations were determined by chemiluminescent immunometric assay using the Immulite 2000 analyser (Diagnostic Product Corporation, Llanberris, Gwynedd, UK). Serum IGF-I was measured by a competitive binding radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Total non-esterified fatty acids (NEFAs) were quantitated by colorimetric assay, using a commercial kit (Alpha Laboratories Ltd, Eastleigh, Hants, UK) and the Cobas MIRA analyser (Roche Diagnostics Corporation, Indianapolis, IN, USA). Body composition (total fat and % fat) was assessed by dual energy X-ray absorptiometry (DXA), using either a Hologic QDR-1000 (Hologic, Waltham, MA, USA) or a Lunar DPX (Lunar, Madison, WI, USA) densitometer. Baseline and follow-up scans were performed on the same instrument for each patient and each instrument underwent daily standard calibration using the appropriate manufacturer's phantom.

Statistical analysis

Baseline (on depot OT) and follow-up (on pegvisomant) serum IGF-I, plasma glucose, NEFAs, total fat, % fat and insulin sensitivity (both HOMA and sITT) were all normally distributed and compared using Student's

Table 1 Clinical characteristics of the seven patients.

Patient no.	Age (years)	Gender	Year of diagnosis	Surgery (year)	Radiotherapy (dose (cGy), year)	Replaced pituitary hormone deficiencies	Dose (mg) and duration (months) of OT therapy
1	46	M	1995	1995, 1996	4500, 1995	None	20, 19
2	76	F	1993	—	—	None	10, 16
3	55	F	1994	1995	3750, 1995	ACTH, FSH/LH	30, 18
4	58	M	1981	—	—	FSH/LH	30, 18
5	61	M	1981	1988	2000, 1988	FSH/LH	30, 19
6	47	F	1988	1988	4000, 1988	ACTH, TSH, FSH/LH	30, 18
7	55	F	1989	1990	4000, 1989	ACTH, TSH	10, 17

paired *t*-test, with statistical significance accepted at $P < 0.05$. A regression analysis was used in order to assess whether the change in either fasting glucose concentration or IS could be predicted by the change in IGF-I between OT and pegvisomant therapies. All values are given as means $\pm$ S.D.

Results

There was no statistically significant change in mean serum IGF-I concentrations between the beginning and conclusion of the study (283 ± 119 ng/ml on depot octreotide vs 191 ± 39 ng/ml on pegvisomant, $P = 0.4$; Fig. 1). Similarly, no change was observed either in total fat ($18\,551 \pm 4571$ g vs $19\,562 \pm 4332$ g, $P = 0.8$) or in % fat ($25.3 \pm 8.1\%$ vs $26.5 \pm 6.9\%$, $P = 0.34$) over the course of the study.

Fasting glucose concentrations were normal (< 6.0 mmol/l) in all seven patients prior to commencement of OT (mean 4.6 ± 0.6 mmol/l). Mean fasting plasma glucose fell from 6.2 ± 1.0 mmol/l on OT to 5.2 ± 0.6 mmol/l on pegvisomant ($P = 0.017$) and was lower on pegvisomant in all seven patients (Fig. 2). In four patients, fasting plasma glucose concentrations fell from values diagnostic of either diabetes mellitus (DM) (≥ 7.0 mmol/l) or impaired fasting

glucose (6.0 – 6.9 mmol/l) to normal on pegvisomant. Mean IS (by sITT) increased from 138.8 ± 38.8 μ mol/l per min on OT to 169.0 ± 55.8 μ mol/l per min on pegvisomant ($P = 0.037$) and improved in six of the seven patients (Fig. 3). Mean IS (by HOMA %S) was unchanged over the course of the study ($155.3 \pm 49.7\%$ on OT vs $139.9 \pm 76.1\%$ on pegvisomant, $P = 0.28$; Fig. 4). Pancreatic β -cell secretory function (HOMA %B) increased significantly on pegvisomant compared with OT ($49.4 \pm 19.2\%$ vs $82.4 \pm 43.5\%$, $P = 0.01$; Fig. 5). There was no statistically significant change in total NEFAs during the course of the study (0.43 ± 0.24 vs 0.40 ± 0.23 mmol/l, $P = 0.35$).

Discussion

In this study, we have documented changes in IS in a group of patients initially treated with conventional, stable doses of a long-acting somatostatin analogue for a median of 18 months (range 16–19 months) and who were then transferred to therapy with the GHR antagonist pegvisomant for a median of 8 months (range 7–9 months). Recognizing the limitations imposed by the non-randomised design of the multi-centre protocol in which the patients were

Figure 1 Serum IGF-I (ng/ml) in seven patients converted from OT to pegvisomant. Values are means $\pm$ S.D.

Figure 2 Plasma glucose concentrations (mmol/l) in seven patients converted from OT to pegvisomant. Values are means $\pm$ S.D.

Figure 3 Peripheral IS ($\mu\text{mol/l per min}$) in seven patients converted from OT to pegvisomant. Values are means $\pm$ s.d.

participating, the study has shown that fasting glucose concentrations were lower on pegvisomant in each of the seven patients, with levels falling to normal from values diagnostic of DM or impaired fasting glucose in four of the seven. There was a significant improvement in peripheral IS, as determined by sITT, but no change in 'whole body' IS, assessed by HOMA analysis. Pancreatic β -cell insulin secretory function (%B) was significantly better on pegvisomant compared with octreotide. These changes in peripheral IS and carbohydrate tolerance occurred independently of changes in total or % fat, as determined by DXA.

Much of the increased morbidity and mortality associated with acromegaly is accounted for by an increased risk of cardiovascular disease (1, 18, 19). Although not definitely proven, it is thought that an important contributory factor to this increased prevalence of vascular disorders (notably hypertension, stroke and diastolic dysfunction leading to congestive cardiac failure) is the increased IR resulting from GH excess. Many of the actions of GH antagonise those of insulin (20): in normal individuals, administration of pharmacological doses of GH leads to hyperinsulinaemia (21, 22), worsens glucose tolerance (21) and reduces glucose uptake into peripheral tissues (22).

In the setting of clinical acromegaly, the diabetogenic effects of GH are clear, judged by the frequency with which impaired glucose tolerance (IGT) and type 2 DM develop in these patients (23, 24). These derangements of IS and glucose tolerance appear to be completely reversible when serum GH concentrations are reduced to 'safe' levels by surgical adenomectomy (25). However, the effect of somatostatin analogue therapy for acromegaly on glucose tolerance is complex and unpredictable (13, 14), owing to the action of this class of drug on endocrine cells other than adenomatous somatotrophs, such as the potent inhibition on insulin and glucagon secretion.

Although the precise mechanisms remain poorly understood, the IR of acromegaly is characterised by defects in the ability of insulin both to suppress hepatic glucose production and by impairment of glucose oxidation and uptake into peripheral tissues (26). Striated muscle is quantitatively the most important tissue for glucose disposal during hyperinsulinaemia (27) and, given that striated muscle is resistant to insulin action in the presence of GH excess (28), a decrease in glucose uptake is likely to be important in the pathogenesis of IGT in acromegaly. This study has clearly shown a significant improvement in peripheral IS in

Figure 4 HOMA analysis of 'whole body' IS (%S) in seven patients converted from OT to pegvisomant. Values are means $\pm$ s.d.

Figure 5 HOMA analysis of pancreatic β -cell secretory function (%B) in seven patients converted from OT to pegvisomant. Values are means $\pm$ S.D.

patients transferred from OT to pegvisomant, judged by the sITT, a technique that provides a robust measure of peripheral IS and which has been well validated against the 'gold standard' hyperinsulinaemic euglycaemic clamp (15). The mechanism for the improvement in peripheral IS is not clear. Peripheral IR in acromegaly is postulated to be due, at least in part, to the lipolytic action of GH, with mobilisation of free fatty acids (FFAs) leading to 'Randle Cycle' substrate competition between glucose and lipid fuels in the periphery (29). The increase in glucose and FFA concentrations in turn leads to insulin secretion and a state of partially compensated hyperinsulinaemia. However, a reduction in lipolysis is unlikely to account for the improvement in peripheral IS demonstrated in this study, as there was no statistically significant change in circulating NEFAs between baseline (on OT) and follow-up (on pegvisomant). Further, although mean serum IGF-I fell during the course of the study, this was not statistically significant ($P = 0.4$) and there was no correlation between the change in serum IGF-I and change in peripheral IS. Beneficial effects on plasma glucose and insulin concentrations were documented in a recent observational study of long-term pegvisomant therapy in acromegaly (10). However, it is important to note that a substantial proportion of patients reported in that study were completely or partially OT resistant, such that the improvement in IS may simply have been consequent upon better biochemical control. The data presented in this study suggest that pegvisomant has a beneficial effect compared with OT on peripheral IS and glucose tolerance independent of the activity of the GH/IGF-I axis. In this context, it is interesting to note that mice expressing a GHR antagonist exhibit increased IS compared with controls and resistance to the development of glucose intolerance when injected with streptozotocin to induce diabetes, suggesting that activation of the GHR leads to altered IS with impairment of glucose utilisation (30, 31).

The improvement in peripheral IS demonstrated is not sufficient to explain the improvement in overall

glucose tolerance, judged by the fall in fasting plasma glucose concentrations in all seven patients (Fig. 2). In acromegaly, the degree of IR *per se* does not predict glucose tolerance, as measurements of IS are equivalent in patients with or without carbohydrate intolerance (17). Compensatory β -cell hyperfunction is seen in those with normal glucose tolerance but not in patients with IGT or DM, indicating that it is β -cell reserve that determines the glucose tolerance state (17). This is supported by the observation that IS improves following surgical adenomectomy (25), whereas pancreatic β -cell reserve is unchanged (17). The fall in fasting plasma glucose concentrations in this study is likely to be due to an improvement in pancreatic β -cell function, suggested by the significant improvement in %B. This, in turn, is likely to be due to withdrawal of the inhibitory effect of OT on insulin secretion, which is not influenced by pegvisomant. Somatostatin and its analogues decrease insulin release both in normal individuals (32, 33) and in patients with GH excess (13, 33, 34). Further, a recent randomised study comparing the effects of OT and pegvisomant on the insulinogenic response to a standard meal documented inhibition of insulin release by OT with consequent postprandial hyperglycaemia (35). Insulin release and plasma glucose levels were not altered by administration of pegvisomant (35). Although the use of somatostatin analogues in acromegaly improves glucose tolerance in some patients by virtue of better control of the GH/IGF-I axis (13, 14), overall, OT therapy is associated with a significant deterioration in glucose tolerance (14). It seems likely, therefore, that increases in both peripheral IS and β -cell secretory function have contributed to the improved glucose tolerance observed in this cohort of patients transferred from therapy with OT to pegvisomant. The reason for the discrepancy between measurements of peripheral (sITT) and 'whole body' (HOMA %S) IS is not clear, but suggests that disturbances of glucose disposal are of particular importance in the development of glucose intolerance in acromegaly.

In summary, these preliminary data suggest that IS and glucose tolerance improve in patients transferred from stable somatostatin analogue therapy to treatment with pegvisomant. Clearly, larger randomized studies in *de novo* patients will be required to clarify this and, if confirmed, to establish the long-term implications of these changes. Endocrinologists can shortly look forward to a time when biochemical control (judged by a normal serum IGF-I concentration) is achievable for virtually all patients with acromegaly. In this context, factors such as convenience of administration, reduction in tumour volume (36) and the effects on IS reported here should all be carefully considered when deciding upon medical therapy for an individual patient.

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