Dose-related effects of growth hormone on IGF-I and IGF-binding protein-3 levels in non-islet cell tumour hypoglycaemia

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Abstract

Mesenchymal tumours are a well recognised cause of spontaneous hypoglycaemia. The mechanism is thought to relate to hypersecretion by tumour cells of high molecular mass insulin-like growth factor-II (pro-IGF-II), with consequent suppression of growth hormone (GH) secretion. The use of recombinant human (rh)GH has been reported to alleviate hypoglycaemia in non-islet cell tumour hypoglycaemia, and the mechanism is thought to relate to GH-mediated increments in serum levels of IGF-binding protein-3 (IGFBP-3), thereby reducing the bioavailability of IGF-II. We report the effect of increasing doses of rhGH on the clinical condition and serum IGF-I and IGFBP-3 levels in two patients with solitary pleural fibrous tumours causing severe hypoglycaemia. Hypoglycaemia was successfully alleviated in each patient although, despite using large doses of rhGH, the observed increments in IGFBP-3 were only modest. We postulate that the beneficial effects of rhGH in this situation are likely to be multifactorial and not simply related to increments in serum IGFBP-3 levels.

Introduction

It has been recognised for several years that certain tumours of mesenchymal origin can cause hypoglycaemia secondary to overexpression by tumour cells of incompletely processed insulin-like growth factor-II (pro-IGF-II), which has a higher molecular mass than normal circulating IGF-II. Hypoglycaemia is usually a late feature of the disease, by which time the prognosis is often measured in months, although occasionally patients may survive for more than a year (1). Alleviation of hypoglycaemia is the overriding clinical problem and treatments successfully employed in this regard include corticosteroids and supraphysiological doses of recombinant human growth hormone (rhGH). Since its original description as a treatment for non-islet cell tumour hypoglycaemia (NICTH) (2), the mechanism of action of GH in this situation has been extensively studied. Its beneficial effects are thought to relate to GH-mediated increases in serum IGF-binding protein-3 (IGFBP-3) levels which, in turn, decrease the bioavailability of IGF-II. We report the clinical characteristics of two patients with NICTH secondary to pleural tumours. Production of pro-IGF-II was documented in each case and hypoglycaemia ameliorated by GH administration. The effect of incremental doses of GH on IGF-I and IGFBP-3 was monitored, and, on the basis of the results, we postulate that the effects of GH in this situation are likely to be multifactorial and not simply due to an increase in IGFBP-3.

Case report 1

A 65-year-old man presented in an acute confusional state resulting from hypoglycaemia (blood glucose 1.9 mmol/l) in association with a suppressed C peptide (Table 1). Several years earlier he had been investigated for a pleural mass diagnosed after difficulties with ventilation during anaesthesia for an inguinal hernia repair. Biopsies of the mass at that time were reported as showing a benign pleural tumour, and he was advised against surgical resection. In the intervening period he had enjoyed good health, although shortly before admission he had developed mild exertional dyspnoea. Examination revealed dullness to percussion with reduced breath sounds over the entire left hemithorax. A computed tomography scan (Fig. 1) showed a large pleural mass causing tracheal compression and deviation of the mediastinum to the right. A 111In-labelled octreotide scan was strongly positive (Fig. 2). Size exclusion chromatography under acid conditions
revealed increased amounts of high molecular mass IGF-II (pro-IGF-II) in the patient’s serum compared with normal control (Fig. 3). During hypoglycaemia, serum levels of cortisol and GH were >600 nmol/l and undetectable respectively.

rhGH was commenced and dose increments made on the basis of fasting glucose measurements. Hypoglycaemia was successfully alleviated with 6 U rhGH a day (mean plasma glucose 1.7 mmol/l at presentation and 3.5 mmol/l after 6 U rhGH daily). Blood samples for assay of IGF-I and IGFBP-3 were taken at each GH dose, and, despite the large doses of rhGH used, the observed increments in IGF-I and IGFBP-3 were only modest (Fig. 4). Prednisolone and octreotide were not used. An attempt was made at debulking surgery, but the patient developed pneumonia and died on the 12th postoperative day.

Case report 2

A 54-year-old man with a known pleural fibrosarcoma subtotally removed on three separate occasions presented with frequent episodes of unrousability and sweating in the early morning. Investigations during hypoglycaemia induced after 6 h of a supervised fast are shown in Table 1. Size exclusion chromatography under acid conditions revealed increased amounts of high molecular mass IGF-II (pro-IGF-II) in the patient’s serum compared with a normal control (Fig. 3). A 111In-labelled octreotide scan showed extensive uptake in the right hemithorax, but hypoglycaemia was worsened by a test dose of 100 μg octreotide given subcutaneously. rhGH was started and the dose titrated against measurements of plasma glucose. Blood samples for assay of IGF-I and IGFBP-3 were taken at each GH dose, and, as with patient 1, despite the large doses of rhGH used, the observed increments in IGF-I and IGFBP-3 were only modest (Fig. 4). During hypoglycaemia, serum levels of cortisol and GH were >600 nmol/l and undetectable respectively. Hypoglycaemia was successfully alleviated for 4 months with 8 U rhGH a day (mean plasma glucose 1.6 mmol/l at presentation and 3.7 mmol/l after 8 U rhGH daily), but had to be increased to 12 U daily, on account of recurrent hypoglycaemia shortly before his death from respiratory failure 5 months after the initial commencement of rhGH.

In neither patient did the clinical condition permit detailed tests of insulin sensitivity or autonomic function during hypoglycaemia.

Methods

Serum IGF-I and IGF-II were measured by standard RIA after formic acid/acetone extraction. The interassay coefficient of variation was less than 10% for both assays (3). Serum IGFBP-3 was measured using an ELISA kit from Diagnostic Systems Laboratories ( Webster, TX, USA). Plasma glucose was measured by the glucose oxidase method. Serum cortisol was assayed on the Bayer Immuno-1 autoanalyser. Plasma insulin and C-peptide were measured by well established and
Figure 3 Identification of IGF-II and pro-IGF-II in serum from patient 1 (left) and patient 2 (right). Elution profiles of immunoreactive IGF-II of serum from the patients and from a normal human serum pool (NHSP) are shown. Samples were analysed by gel filtration chromatography under acid conditions followed by an IGF-II RIA with no cross-reactivity with IGF-I, insulin or proinsulin. The elution position of radiolabelled rhIGF-II (7.5 kDa) used as a marker is indicated in both panels. Increased amounts of pro-IGF-II (approximately 15 kDa; left hand peak) can be seen in both patients.

Figure 4 Effect of rhGH treatment on serum IGF-I and IGFBP-3 levels in patients 1 and 2. Treatment with GH was continuous and the approximate duration of each dose is given at the top.
validated RIAs using the supraregional assay service at the Department of Medical Biochemistry, University of Wales, Cardiff. GH levels were measured by IRMA in the North East Thames Regional Immunoassay Laboratory. All samples assayed by RIA were measured in duplicate.

Patients’ sera and a normal human serum pool (control) were subjected to size exclusion chromatography under acid conditions (4). Briefly, equal volumes of serum and formic acid were mixed and then loaded on to a 1.5 x 100 cm column packed with Sephadex G50 in 0.05 mol/l PBS, pH 7.5. At a pump speed of 6 ml/h, 1 ml fractions were collected approximately every 10 min. The fractions were then neutralised with 145 µl 1 mol/l NaOH, diluted in assay buffer and analysed using an IGF-II RIA with no cross-reactivity with IGF-I, insulin or proinsulin (5). The tracer used for the RIA was 125I iodinated rhIGF-II (Pharmacia, Uppsala, Sweden).

Discussion

Since its original description (2), the use of rhGH in the alleviation of NICTH has been confirmed and reported by others (1, 6). In normal people, IGF-II circulates as a ternary complex of approximately 140 kDa, together with IGFBP-3 and acid-labile subunit (ALS) (7). In NICTH there appears to be inefficient binding of IGF-II of higher molecular mass and IGFBP-3 to ALS (8) such that most IGF-II circulates with IGFBP-3 as a binary complex of approximately 50 kDa, which has a greater hypoglycaemic action than the larger ternary complex. The condition is associated with relative GH suppression, and since expression of IGFBP-3 and ALS is, at least in part, GH dependent, part of the rationale of treating NICTH with rhGH is to increase levels of IGFBP-3 and ALS, thereby promoting the formation of ternary complexes. Teale et al. (6) used supraphysiological doses (4–12 U daily) of rhGH to treat three patients with NICTH and reported significant increases in IGFBP-3 in association with successful alleviation of hypoglycaemia. In contrast, the increments in both IGF-I and IGFBP-3 seen in our patients were modest and consistent with relative GH insensitivity (Fig. 4). Peak IGF-I was within the reference range in patient 2 and just above the reference range in patient 1, despite the use of pharmacological doses of rhGH similar to those described by Teale et al. (6). These blunted changes in IGF-I and IGFBP-3 levels would suggest alternative, possibly direct, mechanisms of action of GH in the alleviation of hypoglycaemia. Although only speculation, likely candidates include stimulation of hepatic glucose-neogenesis and glycogenolysis, both of which would favour increases in plasma glucose in a manner analogous to the induction of glucose intolerance in acromegaly. IGF-II is a partial insulin agonist, promoting glucose uptake by, amongst other tissues, heart, liver and skeletal muscle (9). Counter-regulation of this effect may be an important aspect of the effect of rhGH in the alleviation of NICTH.

Although not used in either of our patients, corticosteroids are another therapeutic option in NICTH. In addition to inhibiting insulin-induced suppression of hepatic glucose production, there is evidence that they promote the formation of the 150 kDa ternary complex of IGFBP-3, IGF-II and ALS, with a consequent reduction in the hypoglycaemic action of IGF-II (1). Steroids were not used in our patients because of concern about long-term side effects, although, in retrospect, the underlying prognosis made this less of an important issue.

There is increasing evidence that long-acting somatostatin analogues such as octreotide have little or no part to play in the management of patients with NICTH. Previously documented cases of NICTH have been associated with variable results from imaging with 111In-labelled octreotide (10, 11), although a recent report of autoradiographic studies on sections of tumour suggested that negative imaging with 111In-labelled octreotide does not exclude the possibility of low levels of expression of somatostatin receptors on the tumour cells (11). To date, there have been no reported cases of a beneficial effect of octreotide on glucose levels in NICTH, and, moreover, in our first patient a test dose of octreotide of 100 µg led to a fall in glucose. The reason for this is not clear, but may relate to further suppression of endogenous GH release from the anterior pituitary.

In summary, NICTH is a challenging clinical problem and, as yet, there is no consensus on the optimum management strategy. It is likely that a combination of rhGH and modest doses of corticosteroids will prove to be most effective in alleviating hypoglycaemia, although the prognosis of the underlying tumour and the presence of co-existent pathologies may influence the decision about the dosage and duration of corticosteroid therapy.

References

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