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CLINICAL STUDIES WITH RECOMBINANT-DNA-DERIVED METHIONYL HUMAN GROWTH HORMONE IN GROWTH HORMONE DEFICIENT CHILDREN

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Summary Thirty-six children with growth hormone deficiency were treated for up to 48 months with methionyl human growth hormone (hGH) synthesised by DNA recombinant methods. The growth rate for these children increased from 3·2±1·1 cm/yr to 10·5±2·2 cm/yr (mean±SD). This was similar to the effect of pituitary hGH in ten GH deficient children, 3·8±1·0 to 10·1±1·1 cm/yr. Serum somatomedin C rose from 0·26±0·23 U/ml to 0·79±0·53 U/ml after 6 months of methionyl-hGH therapy, similar to the effect of pituitary hGH. The incidence of antibody formation to methionyl-hGH was higher than that observed with pituitary hGH (Kabi) but poor growth was observed only in the one patient on methionyl-hGH who acquired high-titre high-binding-capacity antibodies to hGH. No consistent changes in levels of antibodies to *Escherichia coli* proteins were detected. No other allergic manifestations or systemic side-effects were demonstrable.

Introduction

BY means of recombinant DNA techniques, the gene for human growth hormone (hGH) has been expressed in *Escherichia coli* and the methionyl analogue (met-hGH) has been derived and purified.[1-3] The biopotency of purified met-hGH (2 U/mg) is equivalent to that of pituitary-derived hGH (pituitary hGH) in stimulating weight gain, widening the tibial epiphysis, and raising serum free fatty acid concentrations in hypophysectomised rats.[4,5] In adult human beings, met-hGH is equipotent with pituitary hGH in raising plasma somatomedin-C concentrations and in promoting nitrogen retention.[6-8] Likewise, met-hGH is indistinguishable from pituitary hGH in its ability to compete for binding to cell membrane GH receptors and to polyclonal GH antibodies.[6,9]

In October, 1981, clinical trials directed at determining the efficacy and safety of met-hGH as a therapeutic agent were begun in hypopituitary children in 12 US medical centres. This report describes the results of those trials, which now include forty-six children, some treated with met-hGH for as long as 4 years.

Patients and Methods

A total of forty-six children with documented GH deficiency[10] have participated in these trials in which met-hGH is compared with pituitary hGH. Clinical details are shown in table I. All patients were prepubertal at pretreatment examination. None had been treated with GH previously. Depending on time of entry and study objectives, data on three different groups of study patients will be considered:

Group A.—Twenty-two children who were started on met-hGH (G-08 Genentech) between October, 1981, and February, 1982. These patients were switched to a more highly purified met-hGH preparation (G-015) in October, 1983, after 2 months off hGH therapy.

Group B.—Fourteen children who began met-hGH (G-015) in January, 1983.

Group C.—Ten children who began treatment with pituitary hGH (Kabi-Vitrum) in April, 1983.

The study was approved by the ethical committees of the participating medical schools and written consent was obtained from the parents, and from the child when of appropriate age.

The hormone was dispensed in sterile vials containing either 5 mg met-hGH or 2 mg pituitary hGH. Met-hGH was reconstituted by addition of sterile distilled water containing 0·5% benzyl alcohol and pituitary hGH by addition of sterile 0·9% saline. Intramuscular injections of 0·1 mg/kg met-hGH or pituitary hGH were given three times weekly, usually by a parent.

The G-08 and G-015 preparations of met-hGH were both more

than 98% monomeric. They differed in the degree of contamination with *E coli* proteins; the G-08 preparation contained about 200 ppm and G-015 less than 30 ppm.

For up to 1 year before therapy and every 2 months during therapy, growth rates were determined from precise measurements of height by trained observers using wall-mounted stadiometers. At the same outpatient visits, the clinical status was assessed from interval medical history, physical examination, complete blood counts, urine analysis, a comprehensive battery of serum biochemistry tests, plasma somatomedin-C (radioimmunoassay[11]), and measurements of serum antibodies to GH. X-rays of the left hand and wrist with taken every 6 months for assessment of bone age. Bone age was determined from coded films by a trained observer at the Fels Institute, Yellow Springs, Ohio.

Before and after their first three met-hGH injections, the children in group A were given intravenous glucose (0·5 g/kg), after which blood was obtained for measurements of glucose, insulin, and somatomedin-C.

Antibodies to recombinant-DNA-derived hGH were detected and quantitated by a modification of the method of Underwood et al.[12] Briefly, ^{125}I-hGH was incubated with a dilution series of the patients' serum with an initial serum dilution of 1:10. Serum antibodies to hGH were detected by precipitation with polyethyleneglycol. Serum samples were considered positive for antibodies to GH if the percentage binding was twice that observed in control sera. Antibody titres were expressed as the logarithm of the serum dilution at which binding of ^{125}I-hGH was twice that of control sera—ie, binding at a serum dilution of 1:100 was designated as a titre of 2·0. Binding capacity and affinity were determined as previously described.[13]

TABLE I—CLINICAL DATA BEFORE TREATMENT

Group	Sex F/M	Chron age yr*	Bone age yr*	Height −SD for age*	Weight −SD for age*
A	10/12	9·1 (3·3–14·5)	5·4 (1·6–10·7)	−3·7 (−1·5 to −5·0)	−1·6 (+0·1 to −3·5)
B	6/8	8·8 (3·1–13·9)	6·6 (2·1–11·0)	−3·6 (−1·8 to −4·7)	−1·3 (+0·6 to −3·5)
C	4/6	6·1 (4·1–12·2)	5·0 (1·5–11·4)	−3·7 (−2·1 to −5·5)	−1·4 (+0·5 to −3·1)

*Median (range).

Antibodies to *E coli* protein contaminants (ECPs) were detected and quantitated by an immunoradiometric assay developed by Genentech, Inc. Polystyrene 'Removawells' were coated with the ECP preparation obtained from a mock hGH purification process and washed with phosphate buffered saline/0·05% Tween 20. A dilution series of the patient sera (100 µl/well) was added and incubated for 18–24 h at 4°C. After a second wash, 100 µl of ^{125}I-labelled goat anti-human IgM and IgA (17–30 µCi/µg) was added and incubated for 6 h at 4°C. After a final wash the removawells were then counted in a Micro Medic gamma counter. Antibody titre was expressed as the log of the reciprocal of the serum dilution that bound twice the counts observed with a normal serum from which ECP antibodies had been removed by passage over a column of immobilised ECPs. This was necessary to remove the background of these antibodies generated by previous natural exposure to *E coli* antigens.

Results

Growth Responses to GH Therapy

The mean rates of linear growth of children in groups A, B, and C increased threefold during the first year of therapy; no significant differences were evident between groups (table II). Growth rates after the first year fell slightly but equally in all groups. The increase in weight in the three treatment groups was similar (not shown). The mean increment in bone age was consistent with the advancement in chronological age during the first year of therapy in each group. A significant advancement in bone age was seen in groups B and C during the second year (table III).

TABLE II—MEAN (±SD) CUMULATIVE GROWTH RATES (cm/yr)

—	Methionyl hGH Group A n=22	Methionyl hGH Group B n=14	Pituitary hGH Group C n=10
Pretreatment	3·2±1·1	3·2±1·0	3·8±1·0
12 mo	10·5±2·2	10·1±3·0	10·1±1·6
24 mo	7·2±1·9	8·3±2·7	7·1±1·1
36 mo	7·2±1·9		
40 mo	7·3±2·1		

TABLE III—MEAN INCREMENT IN BONE AGE DURING THERAPY

—	Baseline to 12 mo	12–24 mo
Group A (22)	1·3±0·5*	1·1±0·6†
Group B (14)	1·2±0·2	1·7±0·7†
Group C (10)	0·9±0·3*	1·8±1·1†

*p 0·03; †p 0·04 Group A and B; p 0·05 group A and C.

Biochemical Studies

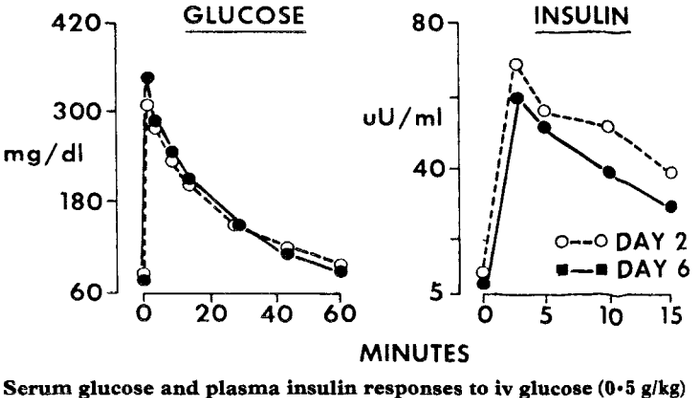
Group A children had an intravenous glucose tolerance test before and after three intramuscular injections of met-hGH (0·1 mg/kg). The peak values of glucose and of insulin did not change (figure).

Plasma somatomedin-C (SMC) increased during GH therapy. In group A, the mean basal SMC rose from 0·26±0·23 U/ml to 0·96±0·72 U/ml after three doses of met-hGH ($p<0·01$); this resembled the effect of pituitary hGH seen in earlier studies[15] (table IV). With prolonged treatment, the increase in SMC in the met-hGH treated children was similar to that of the pituitary hGH treated children.

Four group A children had a decrease in serum total thyroxine and free thyroxine levels after 4 to 12 months of treatment with met-hGH. As expected, a decrease in blood urea nitrogen and an increase in serum phosphorus and alkaline phosphatase was observed in all GH deficient children after administration of either met-hGH or pituitary hGH ($p<0·001$).

Side-effects of GH Therapy

Treatment with met-hGH produced no clinically apparent side-effects. Specifically, there was no febrile response to therapy nor any unusual discomfort at injection sites. No significant changes in serum electrolytes, liver function tests,



Serum glucose and plasma insulin responses to iv glucose (0·5 g/kg) before and after administration of met-hGH.

TABLE IV—PLASMA IMMUNOREACTIVE SOMATOMEDIN C CONCENTRATIONS (SMC) BEFORE AND AFTER ADMINISTRATION OF met-hGH AND PITUITARY hGH

—	Met-hGH Group A	Pituitary‡ hGH
Basal SMC (U/ml)	0·26±0·23	0·27±0·16
SMC generation test*	0·96±0·72	0·84±0·57
—	Met-hGH Group A	Pituitary Group C
Basal SMC	0·26±0·23	0·36±0·3
6 mo†	0·79±0·53	0·98±0·62
12 mo†	1·16±0·64	1·1±1·0
24 mo	1·6±1·0	0·8±0·6
36 mo	2·5±1·9	..

*Sample obtained 20–24 h after 3 daily injections of 0·1 mg hGH/kg.
†hGH, met or pit, 0·1 mg/kg 3 times weekly.
‡Ref 15.

complete blood counts, or urinalyses were observed. Levels of serum *E coli* protein antibody, which is detectable in many normal individuals because of the response to intestinal *E coli*, were not affected by met-hGH therapy (data not shown). There were no clinical signs of allergic diathesis nor was there evidence of complement consumption (assessed by C_3, C_4, CH_{50} measurements or by Raji cell and C_1Q tests for immune complexes).

Twenty-one of the twenty-two group A (met-hGH G-08) patients acquired IgG antibodies to hGH within 4–6 months of the start of therapy. The titres were low in eight (1·6 to 2·0) and higher in thirteen (2·1 to 4·1). In all patients the binding capacities were below the range usually associated with growth attenuation (<7·5 mg/l). When these twenty-one children were changed to the more highly purified preparation (met-hGH G-015), the antibody titre declined in three. Of the fourteen children treated initially with G-015 preparation (group B), five acquired antibodies in low titre (<2·7) and one acquired antibodies in high titre. The ten patients who received pituitary hGH (group C) had no detectable GH antibodies.

In twenty-five of the twenty-six patients who acquired antibody to hGH there was no relation between antibody titre or binding capacity and growth rate (table V). The remaining patient did show growth attenuation: this 14-year-old, who had received radiotherapy and chemotherapy for nasopharyngeal carcinoma, had high-titre antibodies (4·6) with binding capacities of 18–29 mg/l after 1 year of therapy. His growth rate declined to slightly less than 2 cm/yr. When met-hGH was discontinued and treatment with pituitary hGH was begun, his growth rate increased to 8·6 cm/yr over a period of 8 months and his antibody binding capacity fell to 4 mg/l.

TABLE V—RELATION OF ANTIBODY TITRE AND BINDING CAPACITY (BC) TO GROWTH RATE OF CHILDREN TREATED WITH met-hGH

—	Number	Growth rate (cm/yr) mean±SD		
			Treatment period	
		Pretreatment	1 year	2 years
No hGH antibody in pit-hGH patients	10	3·8±1·0	10·1±1·6*	7·1±1·1†
No hGH antibody in met-hGH patients	9	3·1±0·9	10·2±2·9*	8·2±1·8†
Antibody titres >1·5; antibody BC <1 mg/l	15	3·1±1·2	10·8±2·1*	6·7±1·6†
Antibody titres >1·5; antibody BC >1 mg/l	11	3·5±0·8	9·9±2·6*	7·7±2·3†

*,† = no significant differences.

Where titres were high enough to permit study, patient sera were screened for specificity to epitopes directed against the methionyl analogue by means of ^{125}I-met-GH and unlabelled met-hGH. Met-GH-specific antibodies (2–4%) were detected only in the child with growth attenuation during treatment.

Discussion

These results show that met-hGH derived by recombinant DNA techniques has a biopotency equivalent to that of pituitary hGH in promoting linear growth in hypopituitary children.[16-18] Likewise, met-hGH was as effective as pituitary hGH in promoting weight gain, reducing the blood urea nitrogen, increasing the serum phosphorus and alkaline phosphatase,[19] and raising the plasma concentration of somatomedin-C, both in acute and long-term studies.[11,15,20-22] Met-hGH was well tolerated, having no more diabetogenic effect than pituitary hGH[23-25] and producing no increment in serum *E coli* antibodies.

The reduction in serum thyroxine seen in four group A, met-hGH treated, patients is similar to that reported with the use of pituitary hGH.[26,27] We believe, therefore, that this event is generic to GH therapy, and is not specific to met-hGH. The mechanism for this phenomenon is not known.

Other than a higher incidence of antibodies to hGH, no adverse side-effects were observed. We were surprised by the occurrence of hGH antibodies in twenty-one of the twenty-two patients first treated with G-08 met-hGH preparation, because the preparation was highly purified and monomeric. Changes in the purification process gave a met-hGH preparation (G-015) that caused a much lower incidence of antibody formation. While the incidence of antibodies in the G-015 preparation is higher than that seen with pituitary preparations used widely in recent years,[28-31] the antibodies were not associated with signs of complement consumption or formation of immune complexes. Except in one patient, the binding capacity of GH antibodies did not reach the levels that attenuate the growth-promoting action of met-hGH.[14] As described previously, in patients with growth attenuation a change in hGH preparation restores growth.[12,13,31]

Does the additional methionine increase the antigenicity of hGH? Earlier work with polyclonal and monoclonal antibodies to hGH showed no immunological differences between pituitary and methionyl hGH.[6,9,32] Lately, Aston and associates[33] did report differences in antigenicity, as shown by their monoclonal antibody assays; nevertheless, only one of our patients had specific GH antibodies (2–4%) that were directed against met-hGH. Although the G-08 met-hGH preparation was as free of contaminating proteins as the best pituitary hGH preparations available, and the G-015 preparation had even less non-GH protein, it is possible that the imperceptible quantities of *E coli* protein present in these preparations have the capacity to enhance the immunogenicity of the met-hGH, perhaps by an adjuvant effect, without induction of antibodies to *E coli*.

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VERAPAMIL POTENTIATES CARBAMAZEPINE NEUROTOXICITY: A CLINICALLY IMPORTANT INHIBITORY INTERACTION

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Summary Verapamil (120 mg three times a day) was given as adjunctive therapy to six patients with refractory partial epilepsy who were receiving carbamazepine (CBZ). Within a few days symptoms of CBZ neurotoxicity developed in all six patients. There was a mean rise of 46% in total and 33% in free plasma CBZ concentrations in five of these patients ($p<0.01$), and a simultaneous fall of 36% in the ratio of the principal metabolite, CBZ-10,11-epoxide, to CBZ ($p<0.001$). Two patients with mild symptoms were rechallenged with a lower verapamil dosage (120 mg twice a day) and showed similar rises in CBZ concentration and recurrent neurotoxic symptoms. Verapamil increased the area under the CBZ concentration/time curve during a dose interval by 42% in another patient. Withdrawal of verapamil was associated with a decline in circulating CBZ concentration from 12 mg/l to 7 mg/l and seizure breakthrough in a further patient who was receiving both drugs long term. These results suggest that verapamil inhibits the metabolism of CBZ to an extent likely to have important clinical repercussions.

Introduction

DESPITE the best available therapy with anticonvulsant drugs, around 25% of patients with epilepsy are handicapped by recurrent seizures;[1] so new agents are much needed. The mechanisms of action of conventional antiepileptic compounds are complex,[2] but in-vitro studies with phenytoin suggest that neuronal calcium-channel blockade may be important in preventing seizure propagation.[3] Flunarizine, which blocks calcium channels, has shown clinical promise as adjunctive therapy in patients with partial complex seizures,[4] without changing plasma concentrations of existing anticonvulsant medication.

The calcium antagonist verapamil is used widely in the treatment of angina, hypertension, and supraventricular tachycardia.[5] Verapamil penetrates into the cerebrospinal fluid[6] and has shown anticonvulsant efficacy in animals.[7] Its lack of sedative properties[8] makes it attractive as an anticonvulsant. We report here the effect of concurrent verapamil treatment in epileptic patients receiving carbamazepine (CBZ) therapy. The effect of verapamil withdrawal and restoration in a patient receiving both drugs long term is described.

Patients and Methods

Six otherwise healthy patients with refractory complex partial epilepsy and secondary generalised seizures were studied (table I). They had attended our clinical pharmacology clinic regularly for at least a year and were good compliers with consistent steady-state anticonvulsant concentrations. Concurrent medication was not changed during the 3 months before the study. All patients were receiving CBZ 1200–2000 mg/day without subjective evidence of toxic effects; one patient also took phenytoin and one sodium valproate. Each patient gave written informed consent and approval for the study was given by the hospital ethical committee.