Intermittent versus continuous administration of growth hormone treatment

V Hakeem, P C Hindmarsh, C G D Brook

Abstract

Growth hormone treatment given by daily injection was compared with growth hormone given for three weeks of every four. All children had received recombinant human growth hormone for two years before randomisation. Growth velocity decreased in both groups in years one and two of the study but the effect was significantly greater in the group receiving intermittent growth hormone.

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In children with growth hormone insufficiency, the greatest increase in height velocity occurs during the first year of growth hormone treatment. There is a waning of the growth response in subsequent years, and one possible explanation is down regulation of the growth hormone receptor. Attempts to modify the dose and/or the frequency of the treatment regimen have not overcome this effect to any significant degree.^{1,2} Recurrent short periods off treatment might allow the system to 'recover' and thereby avoid tachyphylaxis. We have evaluated this option.

Patients and methods

Twenty six growth hormone insufficient children (20 boys, six girls) aged between 3.9 and 11.1 years were recruited from the paediatric endocrine clinics at the Middlesex Hospital. All had received two years of treatment with recombinant human growth hormone (r-hGH). Patients were randomised to receive intermittent r-hGH treatment (n=13) or continue with daily injections, continuous treatment (n=13). The dose of r-hGH (Genotropin, Kabi Pharmacia,

Stockholm or Norditropin, Novo Nordisk, Gentofte, Denmark) used in the study was 20 units/m² body surface area/week given by nightly subcutaneous injections. For patients receiving intermittent treatment, the total monthly dose of r-hGH was distributed over three weeks, with no r-hGH given during the fourth week, and the cycle was then repeated. Bone age and height velocity were measured for the year before the commencement of the study and annually thereafter, and expressed as SD scores. All children remained prepubertal during the study.

The study was approved by the ethics committee of the Middlesex Hospital and parental consent obtained in all cases.

Student's *t* test was used to compare mean values between the groups and two way analysis of variance (ANOVA) using a repeated measures design was used to compare changes in height velocity within the group.

Results

There was no difference between the two groups at entry to the study in terms of age, height velocity SD score, or height SD score for chronological age (table).

The figure shows the effect of r-hGH on growth velocity over the two year study period. A significant decrease in growth rate was observed in both treatment arms (intermittent, two way ANOVA, $F=10.6$, $p=0.01$; continuous, two way ANOVA, $F=34.6$, $p<0.001$).

Children receiving growth hormone three weeks out of every four weeks grew significantly more slowly during the first (Student's *t* test, $t=3.3$, $p=0.04$) and second (Student's *t* test, $t=3.77$, $p=0.03$) years after the intervention.

Discussion

Animal studies have demonstrated that intermittent growth hormone secretory bursts promote growth more efficiently than continuous exposure.³ In physiological terms, the same is true in man.⁴ However, neither dose nor frequency manipulations are sufficient to prevent the waning of the growth response that occurs after the first year of treatment with r-hGH.^{1,2} Despite allowing time for full receptor sensitivity to reappear,⁵ our alterations to the standard

Endocrine Unit,
Middlesex Hospital,
Mortimer Street, London
W1N 8AA
V Hakeem
P C Hindmarsh
C G D Brook
Correspondence to:
Professor Brook.
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The effects of administering r-hGH by either conventional daily administration (continuous) or intermittently three weeks out of every four on growth rate expressed as a height velocity SD score at entry and after one and two years (bars are SEM).

Anthropometric features of the two groups of children studied. Data shown as mean (SEM)

	Intermittent treatment	Continuous treatment
Age in years	7.9 (0.6)	8.0 (0.5)
Height velocity SD score	2.0 (0.5)	2.4 (0.7)
Height SD score for chronological age	-1.6 (0.2)	-1.0 (0.2)

treatment regimen have not helped. This might relate to compliance with a potentially complex regimen but may relate more to recent studies which have suggested that growth hormone receptor down regulation is rarely seen with the doses of r-hGH used in current clinical practice.⁶

At present, we suggest that daily injections of r-hGH are required for optimal growth in children with growth hormone insufficiency, as repeated interruptions in treatment lead to a compromised growth response.

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Aseptic meningitis caused by human parvovirus B19

A Okumura, T Ichikawa

Abstract

Reports on aseptic meningitis caused by human parvovirus B19 are extremely rare. A case of aseptic meningitis is described in which human parvovirus B19 DNA was detected in the acute phase in cerebrospinal fluid by the polymerase chain reaction.

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Erythema infectiosum is generally a benign, self limiting disease. In 1983 Anderson *et al* found that it was caused by human parvovirus B19,¹ and other pathological manifestations such as aplastic crisis, arthritis, and myocarditis have subsequently been proved to be associated with this virus. We report a case of aseptic meningitis after erythema infectiosum in which virological examination, including the polymerase chain reaction (PCR), for human parvovirus B19 was performed.

Case report

A 7 year old boy developed a bright lacy rash on the cheeks on 28 June 1992; he was afebrile at that time and had no other symptoms. The rash disappeared within a few days. On 4 July, he became febrile and developed a headache. On 7 July, he began to vomit and was admitted to Tokai Chuo Hospital on 8 July.

On admission he was alert. His temperature was 37.5°C and slight neck stiffness was present. There were no skin eruptions. His peripheral white cell count was $4.7 \times 10^9/l$, with 20% band cells, 45% segmented cells, 26% lymphocytes, and 9% monocytes. C reactive protein was 12 mg/l. Cerebrospinal fluid analysis showed a moderate pleocytosis (leucocyte count $112 \times 10^6/l$, neutrophils 61%, mononuclear cells 39%) with a protein concentration of 0.58 g/l, and glucose of 3.3 mmol/l. Routine culture of the cerebrospinal fluid and a throat swab yielded no growth of pathogens.

In a few days the boy became afebrile as well as free of headache and vomiting. Analysis of his cerebrospinal fluid showed a leucocyte count of $9 \times 10^6/l$ with $1 \times 10^6/\mu l$ neutrophils and $8 \times 10^6/\mu l$ lymphocytes; the protein concentration was 0.19 g/l and glucose 3.6 mmol/l. He was discharged on 14 July, and no neurological sequelae have been noted during follow up to October 1992.

SEROLOGICAL STUDIES

Serum and cerebrospinal fluid collected from the patient on 8 and 13 July were tested for human parvovirus B19 (HPV-B19) by enzyme linked immunosorbent assay (ELISA) and the PCR.² Blood contamination was not found at either spinal tap.

The table summarises the ELISA and PCR findings. Serum IgM and IgG antibody against HPV-B19 were positive in both specimens.

Department of Pediatrics, Tokai Chuo Hospital, 4-6-2 Higashijima-cho, Sohara, Kakamigahara, Gifu, Japan, 504 Akihisa Okumura Takayuki Ichikawa

Correspondence to: Dr Okumura.

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Detection of HPV-B19 DNA in cerebrospinal fluid by the PCR. In the 8 July specimen amplification of HPV-B19 DNA was observed, however HPV-B19 DNA was not detected in the 13 July specimen. M: size marker; 1: cerebrospinal fluid of the patient; 2: positive control; 3: negative control (bp = base pair).