# Treatment effects of intranasal growth hormone releasing peptide-2 in children with short stature

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## Abstract

Growth hormone-releasing peptide (GHRP)-2 is a synthetic six amino acid peptide that is a potent GH secretagogue. Although it shares no structural homology with GH-releasing hormone, in clinical studies its actions on the pituitary release of GH are similar. It is effective when administered orally and intranasally. For children with GH deficiency, such noninvasive treatments are most desirable and in need of development. Fifteen children with short stature participated in this study. All of the children had a height <2 s.d. below mean for age, poor height velocity, delayed bone age, and low serum concentrations of IGF-1. These children had been tested with standard GH secretagogues, e.g. arginine, insulin, and L-dopa. Fifty percent of the children were GH deficient, the remainder had idiopathic short stature. The children received testing with GHRH and GHRP-2 as an acute i.v. bolus of 1 μg/kg; all children in this study demonstrated a GH response >20 μg/l. Each child in this study also demonstrated a GH response >10 μg/l in response to intranasal GHRP-2, in the dose range of 5–20 μg/kg. The children were administered intranasal GHRP-2, 5–15 μg/kg, twice a day for 3 months, then three times a day. Fifteen children participated in the study for 6 months; six of the children have participated for 18–24 months. Height velocity, serum IGF-1, IGF-binding protein 3 (IGFBP-3) and GH-binding protein (GHBP) concentrations, and GH responses to GHRP-2 by i.v. bolus and intranasal spray were examined during treatment. Height velocity increased from 3·7 ± 0·2 cm/year to 6·1 ± 0·3 cm/year at 6 months, 6·0 ± 0·4 cm/year at 18–24 months. There were no significant changes in IGF-1 or IGF-PB3 concentrations, or in acute GH responses to i.v. or intranasal GHRP-2. GHBP concentrations rose significantly, from 439 ± 63 pmol/l to 688 ± 48 pmol/l. In this study, intranasal GHRP-2 administration was well tolerated, and produced a modest but significant increase in growth velocity.

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## Introduction

The growth hormone (GH) releasing peptides (GHRP) are a family of synthetic, five to seven amino acid peptides, that selectively stimulate GH secretion (Bowers *et al.* 1984, 1991, Momany *et al.* 1984, Bowers 1993). Although the amino acid sequence is not similar to GH-releasing hormone (GHRH), *in vivo* effects of GHRH and GHRPs on GH release are similar (Bowers *et al.* 1984, 1991). It is well established that GHRPs and GHRH act via different receptors and intracellular signal transduction pathways. However, the mechanisms of action of GHRP remain to be elucidated, especially the hypothalamic action. There is *in vivo* and *in vitro* evidence of direct action on the pituitary somatotrophs as well as on the hypothalamus (Badger *et al.* 1984, Codd *et al.* 1989, 1990, Blake & Smith 1991, Goth *et al.* 1992, Veeraragavan *et al.* 1992, Dickson *et al.* 1993, Fletcher *et al.* 1994). In children and adults, GHRP and GHRH administered together act synergistically to stimulate GH secretion (Bowers *et al.* 1984, Bercu *et al.* 1992). There is some evidence to suggest that endogenous GHRH is permissive with respect to the GH response to GHRP (Blake & Smith 1991, Dickson *et al.* 1993).

The acute GH responses to GHRP-6, GHRP-1 and GHRP-2 have been examined in several animal species (Bowers *et al.* 1991, Davis *et al.* 1994, Cella *et al.* 1995). Being small peptides relatively protected against enzymatic breakdown, the GHRPs are effective via the oral and intranasal as well as i.v. routes of administration. In clinical studies in humans, the most potent GH secretagogue of the GHRP family to date is GHRP-2 (Bowers *et al.* 1984).

Acute GH effects of intranasal and i.v. GHRP-2 and GHRP-6 as well as oral GHRP-6 have been examined in adults and in children of short stature undergoing evaluation for GH deficiency (Bowers *et al.* 1992, Laron *et al.* 1993, 1994, Mericq 1995*a*, Pihoker *et al.* 1995*a*). The responses to either GHRP-6 or GHRP-2 were blunted in children with multiple pituitary hormone deficiencies

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**Table 1** GH responses to arginine, insulin, L-dopa and i.v. GHRP-2, 1 μg/kg. Group A consists of children with GH responses >10 ng/ml to arginine, insulin, or L-dopa; Group B consists of children whose GH responses were <10 μg/l to arginine, insulin and L-dopa

| | Group | Sex | Age (years) | Response to | | | |
|---|---|---|---|---|---|---|---|
| | | | | Arginine | Insulin | L-dopa | GHRP-2 |
| **Patient** | | | | | | | |
| 1 | A | F | 6 | 9·5 | 8·3 | 10·1 | 51·0 |
| 2 | A | M | 6 | 19·0 | — | 13·0 | 52·2 |
| 3 | A | M | 6 | — | — | 17·0 | 48·4 |
| 4 | A | M | 7 | 6·0 | 14·9 | 3·2 | 66·4 |
| 5 | A | M | 8 | 3·0 | 15·3 | 1·0 | 59·6 |
| 6 | A | F | 12 | 13·8 | 8·2 | 8·5 | 86·1 |
| 7 | A | M | 14 | — | — | 10·0 | 47·2 |
| 8 | B | M | 5 | 0·8 | 9·1 | 4·5 | 113·9 |
| 9 | B | M | 5 | 6·6 | 5·6 | 1·5 | 39·2 |
| 10 | B | M | 6 | 4·0 | 9·5 | — | 63·3 |
| 11 | B | M | 8 | 8·2 | 7·7 | 2·6 | 59·2 |
| 12 | B | M | 8 | 1·5 | 1·2 | 0·3 | 21·6 |
| 13 | B | M | 11 | 3·2 | 6·9 | 1·2 | 54·5 |
| 14 | B | M | 11 | 5·7 | 1·4 | 5·8 | 80·3 |
| 15 | B | M | 12 | 7·1 | 5·8 | 0·7 | 96·0 |

and/or a history of cranial radiation therapy. In a recent study, children with isolated GH insufficiency were tested with agents conventionally used, i.e. arginine, insulin, and L-dopa/exercise; in addition, the children were administered i.v. GHRH and GHRP-2. In this group of children, the GH responses to i.v. GHRP-2 were similar to the GH responses observed with i.v. GHRH. Because the diagnosis of GH deficiency is commonly based on results of provocative testing with agents such as arginine, insulin, and L-dopa/exercise, the children were divided into two groups based on their responses to these agents. There were no significant differences in mean GH responses to i.v. GHRP-2 or GHRH between the group of children characterized as GH deficient by standard criteria (GH response less than 10 μg/l) and the group with maximal responses greater than 10 μg/l. To identify the children most likely to benefit from a therapeutic trial of intranasal GHRP-2, children who had a significant GH response to i.v. GHRP-2 were later administered intranasal GHRP-2. Fifteen of sixteen children also had a significant GH response (at least 10 μg/l) to intranasal GHRP-2 at a dose range of 5–20 μg/kg (Pihoker *et al.* 1995*a*).

There are several published reports in which parenteral GHRH has been demonstrated to effectively increase growth rate when administered to GH deficient children (Borkenstein 1986, Thorner *et al.* 1988, Lifshitz *et al.* 1992, Hummelink *et al.* 1993, Low 1993). Multiple daily doses of GHRH, either as multiple injections or via subcutaneous pumps, were more effective than single doses. In a small study, growth velocity was significantly sustained above baseline after discontinuation of GHRH (Lifshitz *et al.* 1992). Effects of chronic GHRP-2 administration on growth and GH dynamics have recently been reported by Pihoker *et al.* (1995*b*) and Mericq *et al.* (1995*b*). Also, Laron *et al.* (1995) reported that the GHRP-6 analog hexarelin increased body growth in short statured children. The efficacy of GHRP-2 as a GH secretagogue combined with the potential for administration via the intranasal and oral routes make it a possibly very desirable alternative to either conventional daily GH injections or GHRH injections. The purpose of this study was to evaluate the safety and growth effects of daily intranasal GHRP-2 administration. The effects on height velocity and biochemical indices of GH secretion were examined. Routine chemistries, blood counts, and thyroid hormone concentrations were monitored. Additionally, growth responses were compared in children grouped according to their GH responses with conventional testing.

## Materials and Methods

Sixteen pre-pubertal children (Tanner stage I), ages 4–12 years (mean age 8 years), undergoing evaluation for short stature participated in an initial study, in which the GH responses to the following agents were examined: i.v. GHRH, i.v. GHRP-2, arginine, insulin, and L-dopa/exercise. All of these children were growing poorly, with a height velocity below the twenty-fifth percentile for age. Heights of the children were at least 2 S.D. below the mean. Serum insulin-like growth factor (IGF)-1 concentration was below the normal range for age in each child. Magnetic resonance imaging studies of the brain (focusing on the hypothalamus and pituitary) were normal in all cases. The GH responses to testing with conventional agents (arginine, insulin, and L-dopa) as well as to

intravenous GHRP-2 are shown in Table 1. Group A consists of children with at least one GH response greater than 10 μg/l to arginine, insulin, and/or L-dopa; Group B consists of children with maximal GH responses less than 10 μg/l on all three tests. All children in this study demonstrated a maximal GH response of at least 20 μg/l to i.v. GHRP-2. The children were then administered intranasal GHRP-2 at a dose range of 5–15 μg/kg (Pihoker *et al.* 1995*a*). Those children with a GH response greater than 10 μg/l were invited to participate in this study. Of the 16 children, only one had a response to intranasal GHRP-2 of <10 μg/l over the dose range of 5–15 μg/kg; that child was excluded from the treatment study.

This study's protocol was approved by the Human Research Advisory Committee of UAMS. Informed consent and patient assent were obtained. The children enrolled in this study received intranasal GHRP-2 twice a day for the first 3 months, then three times daily. Parents were instructed to administer the GHRP-2 doses in the morning, afternoon and at bedtime, with at least 1 h before and after food or medication. Children were given the GHRP-2 for 4-week periods, then were off the GHRP-2 for 1 week. Patients were initially seen monthly, then every 3 months. Blood counts and serum chemistries were obtained on each visit.

Thyroxin ($T_4$) and cortisol were measured by fluorescence polarization immunoassay, and thyroid-stimulating hormone by microparticle enzyme immunoassay, using commercial assays (Abbott Laboratories, Abbott Park, IL, USA) performed at Arkansas Children's Hospital. Serum concentrations of IGF-1, IGFBP-3, and GHBP were measured at Endocrine Sciences (Calabasas Hills, CA, USA). IGF-1 was measured by a competitive binding radioimmunoassay, using a polyclonal sheep antiserum specific for IGF-1 as the primary antibody and radiolabeled synthetic human IGF-1 fragment 57–70 as tracer. Serum IGF-1 was separated from binding proteins by acid–ethanol extraction (Hintz *et al.* 1988, Schwart *et al.* 1996). The extracts were then incubated with primary antibody and tracer. Second antibody, specific for sheep immunoglobulin, was added to precipitate immunocomplexes. Mean intra-assay coefficient of variation (CV) was 5·4%, interassay CV was 7·3%. For IGFBP-3, a high-affinity rabbit primary antibody and radioiodinated IGFBP-3 were mixed with the sample; IGFBP-3 in the sample competed with and displaced tracer from primary antibody. A second antibody, specific for rabbit immunoglobulin, was added to form an immunocomplex, which was separated by centrifugation. Radioactivity in the immunocomplex was counted on a gamma counter. Calibrator samples were used in each assay to establish a standard curve, from which sample IGFBP-3 concentrations were calculated (Baxter & Martin 1986). For this assay, intra-CV was 9%, inter-CV was 11·5%. The GHBP assay was performed using a ligand-mediated immunofunctional assay, in which a monoclonal antibody is used to capture the GHBP on a microtiter plate. GH saturates the binding sites, and an anti-GH antibody is used to detect the amount of endogenous and exogenous GH bound to GHBP (Carlsson *et al.* 1994). Intra-CV was 8·6%, inter-CV was 9·6% for the GHBP assay.

Height was measured using a Harpenden stadiometer and recorded, and height velocity determined at 3-month intervals. Visual inspection of the nasal mucosa was performed by an otolaryngologist at 6 months and at 18 months. The acute GH response to i.v. GHRP-2 was examined at the start and again at 3 months. Also, the GH response to intranasal GHRP-2 was re-examined at 4–6 months. GH was measured using a commercial polyclonal radioimmunoassay (Corning-Nichols Institute, San Juan Capistrano, CA, USA) (Celniker *et al.* 1989). In this assay, serum was incubated with an antibody solution, which contained $^{125}$I-labeled monoclonal anti-hGH antibody (mouse) and biotin-coupled monoclonal anti-hGH antibody (mouse). Avidin-coated beads were added, incubated with serum+antibody solution for 4 h at room temperature, washed twice, and the radioactivity in the pellets counted after all liquid was completely aspirated. The intra-CV was 4·3%, inter-CV was 5·4% for the GH assay.

### *Statistical analysis*

Height velocity, IGF-1, IGFBP-3 and GHBP parameters were compared pre-treatment and during treatment (6 and 24 months), using a repeated measures ANOVA. Mean GH responses to acute i.v. bolus administration at 0 and 3 months were compared, and mean GH responses to intranasal GHRP-2 bolus administration (10 μg/kg) at 0 and 6 months were compared. For these latter comparisons, a nonparametric paired test, the Wilcoxon Signed Rank test, was used. All $P$ values were two-sided. Data were considered statistically significant if the $P$ value was $\leq 0{\cdot}05$. Data are recorded as mean ± S.E.M.

## Results

All 15 children tolerated the intranasal GHRP-2 well, and readily accepted the intranasal spray. Three children complained of a bitter taste in their mouth on occasion after administration of GHRP-2. Parents reported that the amount of solution absorbed appeared to vary from one time to the next, especially when the children had symptoms of upper respiratory infections or allergies. No child experienced any significant adverse effects.

Growth rate increased significantly in most children, with the mean pre-treatment velocity of 3·7 ± 0·2 cm/year and post-treatment velocity of 6·1 ± 0·3 cm/year at 6 months, 6·0 ± 0·2 cm at 18–24 months (Fig. 1). IGF-1 and IGFBP-3 concentrations did not change significantly

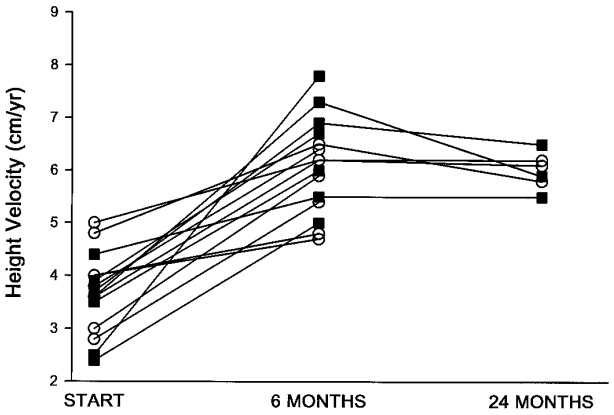


**Figure 1** Height velocity at start, 6 months ($n$=15) and 18–24 months ($n$=6). Group A (children with GH responses >10 μg/l to arginine, insulin or L-dopa) is represented by ■, Group B (children with GH responses <10 μg/l to arginine, insulin and L-dopa) is represented by ○. (Individual patient data presented by each point.)

at any point in the study, but GHBP concentrations were significantly higher at 6 months than pre-treatment (Table 2). Using the Spearman test of rank correlation, the change in GHBP concentrations correlated with the change in growth velocity at 6 months ($r$=0·55, $P$=0·05). The children were divided into two groups, based on their GH responses to L-dopa/exercise, arginine, and insulin. Those children who had a maximal GH response greater than 10 μg/l on any of the three tests were in Group A; the children in whom all GH responses were less than 10 μg/l were in Group B. There were no statistically significant differences between Groups A and B for any of the four growth parameters.

Serum chemistries, serum iron and blood counts remained normal throughout the study. Also, no changes in thyroid hormone, prolactin or fasting cortisol concentrations were observed (data not shown). On direct inspection of the nasal mucosa, no evidence of inflammation was noted.

No significant difference in GH response to bolus i.v. GHRP-2, 1 μg/kg, was observed between initial testing and testing after 3 months of treatment (area under curve (AUC) 60·9 ± 6·3 μg/l × h vs 69·6 ± 19·4 μg/l × h). Similarly, no significant difference in GH responses to intranasal GHRP-2, 10 μg/kg, was observed between initial testing and testing at 4–6 months of treatment, using the ranked sum test (AUC 23·4 ± 5·3 μg/l × h vs 39·5 ± 8·9 μg/l × h). (Data are shown in Fig. 2*a* and *b*.)

## Discussion

Treatment with intranasal GHRP-2 significantly increased the growth rate in these children. The nasal preparation was well tolerated, and no adverse effects were observed. The mean increase in height velocity observed with GHRP-2 was less than that usually observed with initiation of subcutaneous recombinant human GH (rhGH) therapy. Mean growth velocity during treatment was 6·1 cm/year, the same as the expected growth rate in normal pre-pubertal children of the age range in this study. The 'catch-up growth' usually observed with GH therapy was not observed. There are several possible explanations for the modest increase in growth. One explanation is variability in delivery of the GHRP-2. The parents did remark upon apparent inconsistencies in GHRP-2 administration using the nasal spray when symptoms of an upper respiratory infection or allergy were present.

**Table 2** Serum IGF-1, IGFBP-3, and GHBP concentrations at start and 6 months

| | | **IGF-1** (ng/ml) | | **IGFBP-3** (mg/l) | | **GHBP** (pmol/l) | |
|---|---|---|---|---|---|---|---|
| | **Group** | Start | 6 months | Start | 6 months | Start | 6 months |
| **Patient** | | | | | | | |
| 1 | A | 49 | 63 | 1·7 | 2·1 | 232 | 737 |
| 2 | A | 39 | 64 | 1·1 | 2·0 | 631 | 616 |
| 3 | A | 24 | 52 | 1·3 | 1·6 | 728 | 889 |
| 4 | A | 102 | 99 | 2·1 | 2·5 | 226 | — |
| 5 | A | 93 | 108 | 1·8 | 2·0 | 201 | 505 |
| 6 | A | 131 | 116 | 2·5 | 2·0 | 85 | 96 |
| 7 | A | 134 | 115 | 1·4 | 1·9 | — | 639 |
| 8 | B | 70 | 62 | 1·6 | 2·1 | 589 | 661 |
| 9 | B | 37 | 44 | 1·1 | 1·5 | 610 | 664 |
| 10 | B | 46 | 46 | 1·4 | 1·4 | 491 | 643 |
| 11 | B | 40 | 41 | 1·5 | 1·2 | 786 | 523 |
| 12 | B | 156 | 85 | 2·2 | 1·8 | 721 | 562 |
| 13 | B | 144 | 242 | 3·0 | 2·8 | 179 | 1129 |
| 14 | B | 14 | 53 | 0·7 | 0·6 | 94 | 623 |
| 15 | B | 19 | 96 | 1·6 | 1·6 | 382 | 521 |

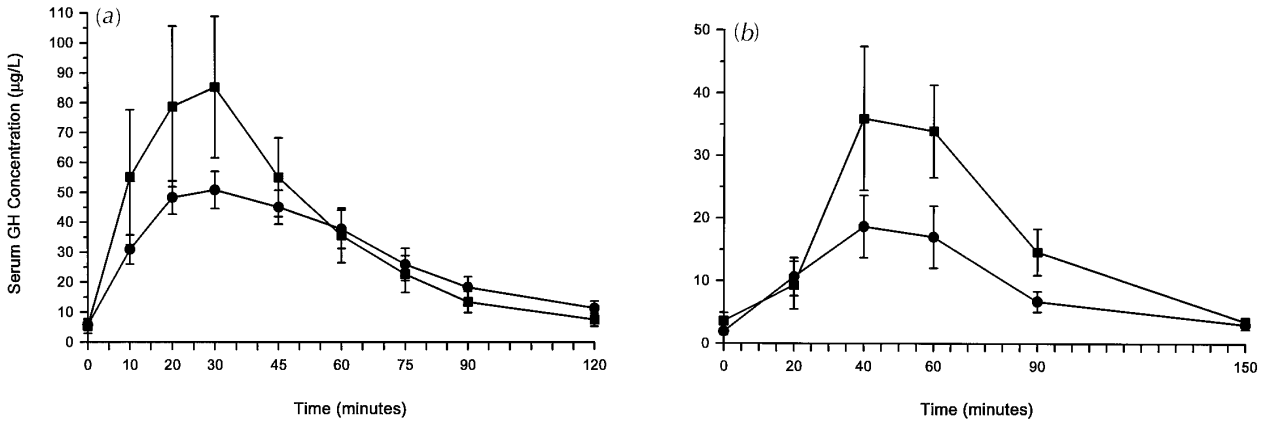


**Figure 2** (*a*) Mean ± S.E.M. GH responses to acute i.v. bolus GHRP-2, 1 µg/kg, on initial testing (●) ($n$=12) and 3 months after daily GHRP-2 administration (■) ($n$=9). (*b*) Mean ± S.E.M. GH responses to an acute intranasal dose of GHRP-2, 10 µg/kg, on initial testing (●) ($n$=12) and 6 months after daily GHRP-2 administration (■) ($n$=9).

Desensitization did not appear to occur, as the GH responses to acute administration of either intranasal or i.v. GHRP-2 did not diminish in these children while on daily GHRP-2 treatment.

There was no significant difference in response to the GHRP-2 either acutely or chronically in children grouped according to results of their GH responses to conventional testing agents, i.e. children who met standard criteria for GH deficiency vs those who did not. All of these children had apparent inadequate GH release or action, in terms of height being greater than 2 S.D. below the mean for age as well as height velocity being less than 25% for age, delayed bone age, and low serum concentrations of IGF-1 and IGFBP-3. The children who had GH responses greater than 10 µg/l in response to arginine, insulin, or L-dopa participated in 12-h overnight GH pulsatile studies. The mean GH concentration was 1·8 µg/l, which was far below the lower limit of normal reported as 3–4 µg/l. These children can be considered to have hypothalamic GH neurosecretory dysfunction. Except for conditions of absolute pituitary GH deficiency, treatment with a GH-releasing agent may represent a more physiologic approach than rhGH replacement. The children in this study, like many children of short stature, can demonstrate pituitary GH release to direct pituitary stimulants, such as GHRH or GHRP, but appear to have abnormal hypothalamic GH regulation. It is possible that these children have a defect in the secretion of GHRH or possibly the putative GHRP hypothalamic hormone, and/or a defect in another neurotransmitter that may work in concert with GHRH or GHRP. GHRP and GHRH act synergistically in adults and in children of short stature; perhaps a combination of GHRH and GHRP-2 would be even more effective in eliciting a growth response than either agent alone.

There was no significant increase in IGF-1 or IGFBP-3 concentration, but GHBP concentrations did increase significantly. Although the nonparallelism between the lack of increase in IGF-1 and the increase in growth velocity is still unclear, similar results have been reported, e.g. with low dose estrogen, GH or GHRH treatment (Copeland 1988, Thorner *et al.* 1988, 1996, Wit *et al.* 1989). It is possible that tissue rather than serum levels of IGF-1 were increased in these children, and/or that tissue responsiveness to IGF-1 was increased. Higher GHRP-2 doses as well as a more efficient intranasal formulation and delivery system might improve the acute and long-term responses to GHRP-2. It appears likely that inconsistencies may have occurred in absorption and bioavailability of the intranasal GHRP-2. Also, the maximum dose used in this study was 15 µg/kg. In a previous study, no significant difference in GH response was observed with doses in the range of 5–20 µg/kg; however, GH responses to higher doses have not been reported. The study was designed such that the children were administered the GHRP-2 daily for 4-week periods, then were off the medication for a week, during which follow-up studies such as chemistries and GH responses to acute bolus i.v. or intranasal GHRP-2 were assessed. Whether this affected the effectiveness of the medication or the fact that no desensitization occurred in our study population remains to be determined.

Another consideration is that the mean GH AUC resulting from administration of intranasal GHRP-2 at a dose of 10 µg/kg was only 14% of the mean GH AUC achieved with a subcutaneous injection of rhGH, using a standard dose of 0·043 mg/kg (22 vs 152 µg/l × h) (Kearns *et al.* 1991). Administering two or three doses of GHRP-2/day, the total GH AUC produced with intranasal would still be considerably less than that observed with subcutaneous rhGH at a dose of 0·043 mg/kg per day. It is estimated that the commonly used dose of rhGH of 0·043 mg/kg per day is approximately three times the physiologic secretion of GH (Kearns *et al.* 1991). The initial, early growth response to rhGH is in the range of

8–10 cm/year for the first year of treatment, which is greater than the normal growth velocity for pre-pubertal children. Perhaps one of the reasons that the growth response to intranasal GHRP-2 observed is approximately 6 cm/year is that the GH secretion achieved during the first year is closer to the physiologic secretion of normal pre-pubertal children, thus producing a growth velocity closer to that observed in normal pre-pubertal children.

This was not a double-blind placebo-controlled trial. Modest short-term increases in growth velocity have been observed with other GH stimulatory agents such as clonidine or sometimes with no treatment and observation only (Pintor *et al.* 1987). A higher and/or more sustained GH response may be needed to produce the catch-up growth response. Such might be possible with an agent which takes advantage of the synergy between GHRH and GHRP-2. With newer GH-releasing agents, such as the GHRP mimetic MK-0677 developed by the Merck group, the GH profile produced by MK-0677 is longer in duration, and increases in IGF-1 have been observed in short-term treatment of adults (Bach *et al.* 1996).

Since the catch-up growth response induced by rhGH occurs within the first year or even within 3–6 months of starting rhGH treatment and is restricted to this time period of treatment, in future studies it may be possible and desirable to induce catch-up growth with rhGH and once achieved, substitute GHRP-2 for the rhGH as a more acceptable long-term therapy. It is well established that all of the GHRPs so far developed, including MK-0677, act in the same way to release GH. The fact that the peptide mimetic GHRP, MK-0677, more readily raises serum IGF-1 levels appears to indicate the important role of the pharmacokinetics of the GHRPs. The shorter serum half-life of GHRP-2 and longer half-life of MK-0677 may be the major reason for the difference in serum IGF-1 levels. Additionally, these pharmacokinetic differences help to emphasize the importance of the continued optimization of the GHRP treatment approach and that the suboptimal body growth response induced by GHRP-2 may be more of a technical issue rather than an issue of principle.

The increase in GHBP, along with the increase in growth velocity, suggests that physiologic changes were induced on the GH axis by GHRP-2. GHBP has been reported to increase acutely with GH treatment. There have been discrepancies reported in terms of the effects of long-term GH enhancement on serum GHBP concentrations, e.g. increased or unchanged (Martha *et al.* 1992, Mandel *et al.* 1995, Saggese *et al.* 1995, Kempe 1996). In this study, GHBP concentrations did increase at 6 months, then appeared to stabilize at the higher level. The initial increase in GHBP was statistically correlated with the increase in growth velocity.

As many children with GH deficiency respond well to GH-releasing factors such as GHRH, GHRP-6 or GHRP-2, testing with GHRP-2 may or may not be helpful in identifying those children with GH insufficiency. To possibly develop and assess the future potential value of a GHRP-2 or GHRP-2+GHRH diagnostic test for children will require not only a more complete understanding of the hypothalamic action of GHRPs but also further insight into the pathophysiology of decreased secretion of GH in children with short stature. By utilizing GHRP, GHRH and these peptides in combination and at different dosages, it may be possible to reveal a qualitative as well as a quantitative difference in these children that more directly relates to the pathophysiology. Administration of combined GHRP and GHRH (1 μg/kg of each peptide) would enable assessment of pituitary GH secretory capacity. There are nonpeptidyl GH-releasing agents being developed which also selectively stimulate GH secretion (Patchett *et al.* 1995, Bach *et al.* 1996). In clinical practice, the populations most likely to benefit from treatment with a growth hormone secretagogue are those with adequate pituitary reserve but inadequate GH release. Such children appear to comprise the majority of cases of isolated GH deficiency.

In summary, treatment with intranasal GHRP-2 produced a significant but modest increase in growth rate in this group of children. The GHRP-2 was well tolerated. At present the factor(s) contributing to the modest increase in height velocity and the lack of rise in IGF-1 and IGFBP-3 concentrations remains to be determined. Future studies aimed at studying possible central and peripheral factors which may improve the effectiveness of GH releasing agents are needed. Also, a method of producing a more sustained GH response when GHRP-2 is administered may improve the growth response.

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