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Original Article

Increased Secretion of Endogenous GH after Treatment with an Intranasal GH-releasing Peptide-2 Spray Does Not Promote Growth in Short Children with GH Deficiency

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Abstract. We investigated whether treatment with an intranasal GH-releasing peptide (GHRP)-2 spray, which acts as a potent GH secretagogue that stimulates endogenous GH secretion, promotes growth in patients with GH deficiency (GHD). This study involved 126 prepubertal short children (81 males, 45 females) with a height SD score of –2 SD or less, who had been diagnosed as having GHD based on GH stimulation tests, and in whom the serum GH concentrations increased up to 9 ng/ml after preliminary administration of an intranasal GHRP-2 spray. The subjects included in this study were divided into 3 groups by use of a double-blind method; that is 44 were placed into the placebo group (P group: 30 males, 14 females), 41 were placed into the GHRP-2 low dose group (L group: 25 males, 16 females), and 41 were placed into the GHRP-2 high dose group (H group: 26 males, 15 females). Those with a body wt of less than 20 kg were administered a placebo (P group), 50 μg of GHRP-2 (L group) or 100 μg of GHRP-2 (H group), and those with a body wt of 20 kg or more were administered a placebo (P group), 100 μg of GHRP-2 (L group) or 200 μg of GHRP-2 (H group) twice daily (morning and evening) for 48 continuous wk. Age and height SD scores at baseline were not significantly different among the three groups: 7.5 yr old and –2.26 SD in the P group, 7.3 yr old and –2.38 SD in the L group, and 7.5 yr old and –2.27 SD in the H group. Of the 126 subjects, 44, 40 and 40 subjects in the P, L and H groups, respectively, completed the 48 continuous wk of treatment. The changes in the mean height SD scores (mean growth rate) after 48 wk of treatment in the P, L and H groups were 0.07 SD, 0.03 SD, and 0.02 SD, respectively, and thus no significant differences was observed among the 3 groups. Also no significant changes in blood IGF-I levels at baseline or after 48 wk of treatment were observed among the 3 groups. This study revealed that in patients with GHD, an increase in endogenous GH secretion as a result of treatment with GHRP-2 does not promote growth. It is speculated that the area under the curve of serum GH concentration by GHRP-2 spray is too small to produce biological effects. In conclusion, it was demonstrated that growth cannot be promoted by a transient increase in endogenous GH secretion.

Key words: endogenous GH, GH deficiency, intranasal GHRP-2 spray

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Introduction

In the late 1970s, Bowers *et al.* developed an artificial peptide that consists of 6 amino acids derived from methionine-enkephalin, acts as a GH secretagogue (GHS) and promotes the secretion of GH. Since then, various GHS have been synthesized, and in 1992, Bowers *et al.* prepared GH releasing peptide-2 (GHRP-2, KP-102: generic name pralmorelin hydrochloride), which is a potent peptide compound (1).

GHRP-2 effectively promotes GH secretion and is also approved in Japan as a diagnostic agent for severe adult GH deficiency (AGHD) and GH deficiency (GHD) in short children. Its cut-off value is 9 ng/ml for AGHD and 16 ng/ml for short children with GHD and thus is higher than that of the agents used for the GH secretion stimulation test for AGHD (1.8 ng/ml) (2) and for short children with GHD (6 ng/ml).

However, only a poor increase in the serum GH concentration is observed when GHRP-2 is administered orally due to the effects of food intake, and therefore, an intranasal GHRP-2 spray was developed. In 1997 Pihoker *et al.* (3) reported that, in 15 children with short stature (7 with idiopathic short stature, 8 with GHD) who showed peak GH levels >20 ng/ml after intravenous administration of GHRP-2 (1 μg/kg) and peak GH levels >10 ng/ml after administration of an intranasal spray preparation (5 to 15 μg/kg), a therapeutic effect was observed after 18 to 24 mo when the nasal spray was administered twice daily (5 to 15 μg/kg/dose) for a period of 3 mo and thereafter 3 times a d. As a result of the treatment with intranasal GHRP-2 spray, no changes in the serum IGF-I and IGF-BP-3 levels were observed, and the growth rate increased significantly from 3.7 ± 0.2 cm/yr at baseline to 6.1 ± 0.3 cm/yr after 6 mo of treatment; the authors concluded that the intranasal GHRP-2 spray is a promising agent for treatment of GHD. However, we could not find any other reports on its clinical usefulness that were published after this report.

Here we report the results of a double-blind clinical study that involved 126 children with GHD and was conducted for a period of 1 yr to investigate the growth promotion effect of an intranasal GHRP-2 spray.

Subjects and Methods

This study included 84 facilities throughout Japan and involved 126 children (81 males, 45 females) who fulfilled the following criteria: 1) prepubertal boys aged ≥4 to <10 yr old, and prepubertal girls aged ≥4 to <9 yr old; 2) a height SD score of –2 SD or less and peak GH levels of 6 ng/ml or less in at least 2 GH stimulation tests using insulin, glucagon, arginine, clonidine or L-DOPA (4); 3) an increased in the serum GH level to at least 9 ng/ml more than 30 or 45 min after administration in a preliminary test in which the subjects were administered an intranasal GHRP-2 spray (50 μg in those with a body wt of less than 20 kg, and 100 μg in those with a body wt of 20 kg or more).

All subjects had been diagnosed as having idiopathic GHD. According to the maximum peak GH value in the GH stimulation tests (mpGH), the subjects were classified into three types of GHD as follows: 15 patients with severe GHD (mpGH ≤ 5 ng/ml), 111 patients with moderate GHD (5 ng/ml < mpGH ≤ 10 ng/ml) and 46 patients with mild GHD (mpGH > 10 ng/ml). However, there were no difference in height SDS, serum IGF-I concentrations and growth velocity among the three types of GHD.

Subjects were enrolled by a double-blind method into 3 groups; that is 44 were included in the placebo group (group P: 30 males, 14 females), 41 were included in the GHRP-2 low dose group (group L: 25 males, 16 females), and 41 were included in the GHRP-2 high dose group (group H: 26 males, 15 females). Background and clinical factors of the subjects at baseline are presented for each group in Table 1. No significant differences in conditions at birth, height of parents, mpGH, age, height, body wt,

Table 1 Clinical characteristics among three groups of GHRP-2 doses

	Group P (44)	Group L (41)	Group H (41)
Male/female	30/14	25/16	26/15
Gestational wk (wk)	38.5 ± 2.6	38.4 ± 2.8	38.2 ± 3.4
Birth wt (g)	2674 ± 543	2620 ± 623	2708 ± 657
Birth length (cm)	46.9 ± 2.8	46.5 ± 4.6	47.1 ± 3.9
Father's height (cm)	167.6 ± 5.3	167.9 ± 5.6	167.1 ± 4.9
Mother's height (cm)	153.1 ± 5.9	153.2 ± 4.4	153.4 ± 4.5
Maximum GH peak (ng/ml) by GH stimulation tests	7.1 ± 5.5	7.0 ± 5.0	6.5 ± 3.6
Maximum GH peak (ng/ml) by nasal GHRP-2 spray	16.2 ± 7.5	14.6 ± 5.3	16.7 ± 5.8
At the sart of treatment			
Age (yr)	7.5 ± 1.5	7.3 ± 1.7	7.5 ± 1.9
Height (cm)	110.4 ± 7.7	108.2 ± 9.4	109.7 ± 10.6
Wt (kg)	18.7 ± 3.7	17.7 ± 3.6	18.5 ± 4.5
Height SD score (SD)	–2.26 ± 0.36	–2.38 ± 1.33	–2.27 ± 0.34
Growth velocity (cm/yr)	5.3 ± 0.7	5.2 ± 0.9	5.3 ± 0.7
IGF-I (ng/ml)	127.7 ± 45.1	122.7 ± 43.8	131.9 ± 52.8

height SD scores, annual growth rate or serum IGF-I concentrations were observed among the 3 groups.

The peak GH values obtained in the groups P, L and H after preliminary treatment with the intranasal GHRP-2 spray were 16.2 ± 7.5 ng/ml, 14.6 ± 5.3 ng/ml and 16.7 ± 5.8 ng/ml, respectively, and thus there were no significant differences among the 3 groups. The GHRP-2 spray was obtained from Kaken Pharmaceutical Co., Ltd. (Bunkyo-ku, Tokyo, Japan).

The subjects in group P received a placebo, while those in the other two groups were administered the intranasal GHRP-2 spray twice a day, in the morning before meals and in the evening before bedtime; for these two groups, subjects with a body wt of less than 20 kg were administered 50 μg (group L) or 100 μg (group H), and those with a body wt of 20 kg or more were administered 100 μg (group L) or 200 μg (group H). At the start of treatment, and after 24 and 48 wk of treatment with the intranasal GHRP-2 spray, blood was collected before administration and at 30, 45 and 60 min after administration to determine serum GH concentrations. The GH concentration was plotted against time, and the area under the curve (AUC) of the GH concentration was calculated as the sum of trapezia of the area under the GH concentration line.

Serum IGF-I concentrations were determined before initiation of treatment and after 24 and 48 wk of treatment. Height and body wt was measured at the start of treatment and after 4, 12, 24, 36 and 48 wk of treatment.

For comparisons between the groups, the Games-Howell test was performed.

This clinical study was conducted at the request of Kaken Pharmaceutical Co., Ltd., after obtaining approval from the ethics committees of each participating facility and written consent from a parent or guardian of each subject in compliance with the GCP guidelines.

Results

Of the 126 subjects, 44, 40 and 40 subjects in groups P, L and H, respectively, completed the 48-wk treatment period. None of the subjects reached puberty during the treatment period. The values that were determined are not shown separately for boys and girls, since no differences in measured values were observed between them.

The mean peak serum GH values at baseline and after 24 and 48 wk of treatment with the intranasal GHRP-2 spray (group P received

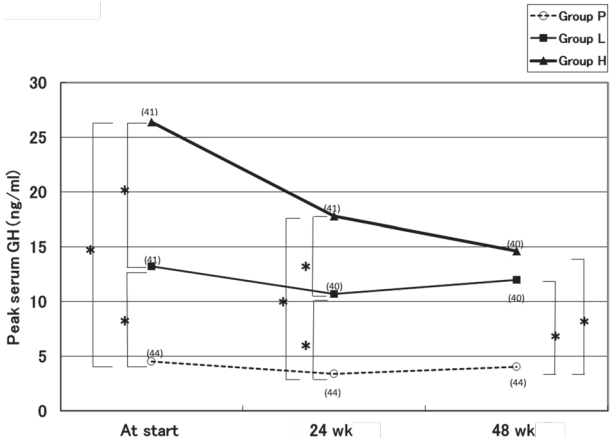

Fig. 1. Mean peak serum GH concentrations after administration of the GHRP-2 nasal spray at the start of treatment and at 24 wk and 48 wk of treatment in three groups of GHRP-2 doses. Numbers of subjects are shown in parentheses. *p < 0.05.

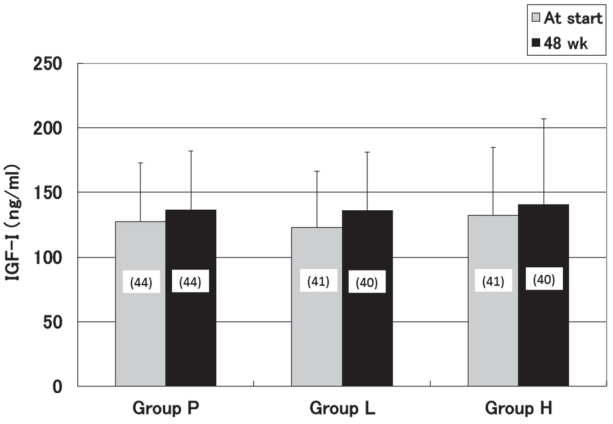

Fig. 2. Mean serum IGF-I concentrations before the GHRP-2 treatment and 48 wk after treatment in three groups of GHRP-2 doses. Vertical bars indicate the SD. Numbers of subjects are shown in parentheses.

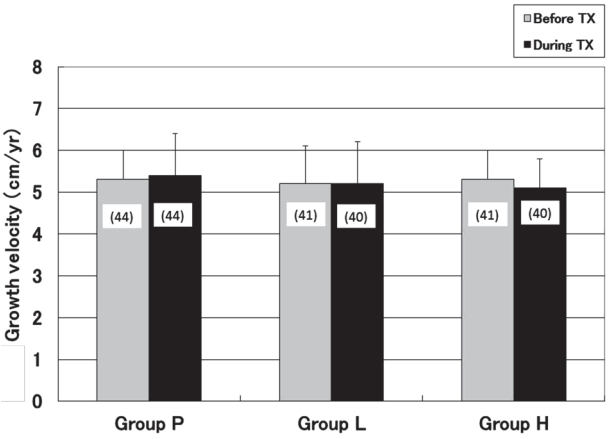

Fig. 3. Growth velocity before and during the 48 wk of treatment. Vertical bars indicate the SD. Numbers of subjects are shown in parentheses.

a placebo) are shown for each group in Fig. 1. At baseline, the mean peak serum GH values were 4.5 ng/ml in group P, 13.2 ng/ml in group L, and 26.4 ng/ml in group H, and thus significant differences were observed among the 3 groups. After 24 wk of treatment, the mean peak serum GH values were 3.4 ng/ml in group P, 10.7 ng/ml in group L, and 17.8 ng/ml in group H, and thus significant differences were also observed among 3 groups at this time point. However, the mean peak GH values of groups L and H gradually decreased, and after 48 wk of treatment, the mean peak serum GH values were 4.0 ng/ml in group P, 12.0 ng/ml in group L, and 14.6 ng/ml in group H; thus no significant difference was observed between groups L and H.

At baseline, the mean AUC values were 1.94 ng/ml・hr in group P, 8.3 ng/ml・h in group L and 16.3 ng/ml・h in group H.

The changes in the serum IGF-I levels are shown in Fig. 2. No significant differences were observed among the 3 groups, and no significant changes were observed in any of the 3 groups during the 48-wk treatment period. Growth rates (cm/yr) during the 1 yr before the start of treatment and during the 48-wk treatment period are shown in Fig. 3. During treatment, the mean growth rates in groups P, L and H were 5.4 cm/yr, 5.2 cm/yr and 5.1 cm/yr, respectively, and thus no significant differences were observed; no promotion of the growth rate was observed as result of treatment.

After 48 wk of treatment, the height SD scores in groups P, L and H were –2.18 SD, –2.35 SD, and –2.24 SD, respectively, and thus no significant differences were observed among

3 groups: also no significant change in height SD score was observed in any of the 3 groups as result of treatment.

Adverse events were reported for 76 subjects (60.3%), and most of the adverse events were accidental such as acute upper respiratory tract inflammation, tonsillitis and otitis media; adverse events that were judged by the investigator as "possibly related" or "probably related" included borborygmus (in 3 subjects) and epistaxis, decreased blood pressure and eosinophilia (in the same subject).

Discussion

This study involved subjects with idiopathic GHD, in whom decreased GH secretion had been confirmed by commonly used GH stimulation tests. However, since treatment with the potent intranasal GHRP-2 spray was confirmed to substantially increase GH secretion, we believe that this was a population of children with short stature in whom the ability to secrete GH was not severely impaired. Since there were no significant differences in clinical characteristics among the subjects with three types of GHD, it was suggested that their GH secretion capacities were not severely impaired, even in those with severe GHD. Classically, severely short children who were born by breech presentation and with asphyxia were diagnosed as having severe GHD with other pituitary hormone deficiencies and showed a decreased growth velocity and low IGF-I levels. However, nowadays babies with a breech presentation are born by Cesarean section. We classified short children as having severe GHD based on mpGH. But severe GHD did not show a decreased growth velocity and low IGF-I levels in this study, and therefore the subjects with severe GHD were clinically different from those with classical severe GHD. This fact demonstrated the uncertainty of GH stimulation tests in the diagnosis and classification of GHD as previously pointed out (5). Patients with brain tumors, such as craniopharyngioma, can be diagnosed as having severe GHD and usually show a very low mpGH. It might be better to revise the cutoff point for severe GHD to be a lower concentration of mpGH. The data in the present study were presented for boys and girls together, since no differences were observed between them. Furthermore, all subjects were prepubertal throughout the study. During the prepubertal period, the differences between boys and girls are minimal in terms of growth velocity, IGF-I levels and response to GH treatment in GHD.

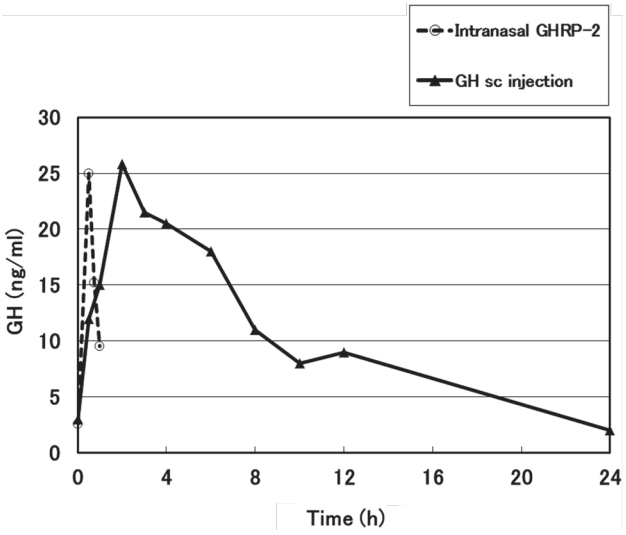

Fig. 4. Mean serum concentration after administration of nasal spray and subcutaneous injection of GH.

Although the peak GH values after treatment with the intranasal GHRP-2 spray tended to decline slightly in group H and did not change much in group L during this clinical study, the GH values in groups H and L were significantly higher than in group P. However, even in groups H and L, no significant increase in IGF-I value was observed, and no improvement in the growth rate was observed after 1 yr of treatment.

Figure 4 shows the changes in the mean GH concentrations after treatment by subcutaneous GH injection (25 μg/kg) (6) and the intranasal GHRP-2 spray in group H at the time when this clinical study was initiated. GH was subcutaneously injected into 12 short children

(9 boys, 3 girls) aged from 6 yr to 12 yr (6). With these administration methods, high peak GH concentrations of 25.8 ± 3.1 ng/ml and 25.0 ± 15.8 ng/ml, respectively, were achieved, and there were no differences in the mean peak serum GH concentrations. However, the AUC was found to be much smaller during treatment with the intranasal GHRP-2 spray in group H (16.3 ± 10.0 ng/ml • h) than that during treatment with subcutaneous GH injection (230 ± 7.0 ng/ml • hr) (6), although concentrations were measured at different time points. When treatment is conducted by subcutaneous GH injection, the exogenous GH inhibits endogenous GH (7), and therefore, the dose that is injected should be an amount that is sufficient to maintain the serum GH concentration over a prolonged period of time and to promote growth by stimulating the production of IGF-I. The intranasal GHRP-2 spray stimulated a prompt GH discharge from the pituitary, but GH secretion did not continue. It is speculated that the effect of the GHRP-2 spray on the AUC of the serum concentration is too small to produce biological effects.

One could argue that twice a d administration of the spray is not enough to mimic the physiological GH secretion and that more frequent administration may be effective in increasing the AUC and serum IGF-I and promoting improvement of the growth velocity. When the AUC is taken into account, more than 10 times as much nasal spray is necessary to increase the AUC amount to be close to that caused by subcutaneous injection. Although physiological GH secretion is mainly observed during sleep in prepubertal children, frequent intranasal GHRP-2 administration during sleep is a clinically impossible means of mimicking physiological GH secretion. Moreover, it seems doubtful that the serum GH level would increase up to 25 ng/ml after every administration of the GHRP-2 spray.

Although we had expected that treatment with GHRP-2 would sufficiently stimulate the secretion of endogenous GH and promote growth because of the strong GH secretion-inducing properties of GHRP-2, no growth promoting effect was observed. We may have obtained different results from those reported by Pinhoker *et al.* (3) because the subjects in their study (3) had a lower growth rate before the start of treatment and the proportion of subjects with severe GHD was higher. Furthermore, 5 of the subjects were children with short stature who were 10 yr of age or older, and thus it is possible that the growth observed in those children during the GHRP-2 treatment overlapped with the growth spurt of puberty. Pinhoker *et al.* (3) also were not sure why the growth rates increased in their subjects without an increase in the IGF-I level. It is possible that no other clinical trials have been performed using GHRP-2 for growth promotion for the following reasons. Even if the growth rate was improved with this treatment, at the utmost, a mean growth rate of 6.1 cm/yr was achieved (3). This growth rate is comparable to the prepubertal growth rate of healthy children, and this improvement is considered poor compared with the mean growth response of 8 cm/yr in children with GHD treated with GH in the first yr.

Among the various attempts to promote the growth of children with short stature by increasing endogenous GH secretion, in addition to GHRP-2 (3), treatment with intravenous injection of GH-releasing hormone (GHRH) (8, 9) has been reported, but due to difficulties in administration, it has not been possible to apply this method in a clinical setting. Furthermore, an oral treatment with clonidine was reported to be effective in one study (10); however, this treatment was found to be inefficient in subsequent studies (11, 12).

At present, medications and supplements that may increase endogenous GH secretion and promote growth can be found in abundance on the Internet. A typical example is arginine. Arginine is used for the GH stimulation test, in which 0.5 g/kg of arginine is administered by intravenous drip infusion for 30 min to

increase the blood arginine concentrations and stimulate GH secretion. Therefore, in the case of children weighing 30 kg, 15 g of arginine is infused. It is unlikely that the blood arginine concentration after oral administration of 2 to 3 g of arginine is capable of increasing GH secretion and promoting growth. Even though endogenous GH was sufficiently stimulated in the present study, no growth promotion effect was observed.

Therefore, it is necessary to issue a warning about the use of medications and supplements that can be found in abundance on the Internet and claim to promote GH secretion. The Japanese Society for Pediatric Endocrinology has set up a homepage for this purpose titled "Opinion of the Japanese Society for Pediatric Endocrinology with regard to warning patients about the use of supplements, etc., that claim to increase height."

In conclusion, it was demonstrated that growth cannot be promoted by a transient increase in endogenous GH secretion.

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