0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 83, No. 4
Printed in U.S.A.

Pharmacokinetics and Pharmacodynamics of Growth Hormone-Releasing Peptide-2: A Phase I Study in Children*

CATHERINE PIHOKER, GREGORY L. KEARNS, DANIEL FRENCH, AND CYRIL Y. BOWERS

Department of Pediatrics, University of Washington (C.P.), Seattle, Washington 98105; the Departments of Pediatrics and Pharmacology, University of Missouri (G.K.), and the Section of Pediatric Clinical Pharmacology and Experimental Therapeutics, Children's Mercy Hospital (G.K.), Kansas City, Missouri 64108; Wyeth-Ayerst Research (D.F.), Princeton, New Jersey 08543; and the Department of Medicine, Tulane University School of Medicine (C.B.), New Orleans, Louisiana 70112

ABSTRACT

Administration of GH-releasing peptide-2 (GHRP-2) represents a potential mode of therapy for children of short stature with inadequate secretion of GH. Requisite information to determine the dosing route and frequency for GHRP-2 consists of the pharmacokinetics (PK) and pharmacodynamics (PD) for this compound, neither of which have been previously evaluated in children. The purpose of this study was to characterize the PK and PD of GHRP-2 in children with short stature. Ten prepubertal children (nine boys and one girl; 7.7 ± 2.4 yr old) received a single 1 μg/kg iv dose of GHRP-2 over 1 min, followed by repeated (n = 9) blood sampling over 2 h. GHRP-2 and GH were quantitated by specific RIA methods. PK parameters were calculated from curve fitting of GHRP-2 and GH *vs.* time data. Posttreatment plasma GH concentrations (normalized for pretreatment values) were used as the effect measurement. PD parameters were generated using the sigmoid E_{max} model. Disposition of GHRP-2 best fit a biexponential function. GHRP-2 PK parameters (mean ± SD) were: α = 13.4 ± 9.7 h^{-1}, β = 1.3 ± 0.3 h^{-1}, $t_{1/2\beta}$ = 0.55 ± 0.14 h, $AUC^{0\rightarrow\infty}$ = 2.02 ± 1.37 ng/mL·h, C_{max} = 7.4 ± 3.8 ng/mL, plasma clearance = 0.66 ± 0.32 L/h·kg, and apparent volume of distribution = 0.32 ± 0.14 L/kg. PK parameters for GH were: appearance rate constant = 5.9 ± 3.1h^{-1}, elimination $t_{1/2}$ = 0.37 ± 0.15 h, lag time = 0.05 ± 0.01 h, C_{max} = 50.7 ± 17.2 ng/mL, T_{max} = 0.42 ± 0.16 h, and $AUC^{0\rightarrow\infty}$ = 47.9 ± 26.1 ng/mL·h. PD parameters for GHRP-2 were: K_{e0} = 1.13 ± 0.94 h^{-1}, γ = 13.15 ± 9.44, E_0 = 6.63 ± 4.86 ng/mL (GH), E_{max} = 67.5 ± 23.5 ng/mL (GH), and EC_{50} = 1.09 ± 0.59 ng/mL. We concluded that 1) GHRP-2 produced a predictable and significant (*i.e.* compared to pretreatment values) increase in plasma GH concentrations; 2) the PK-PD link model enabled quantitative assessment of GHRP-2 modulation of serum GH levels; and 3) definition of the EC_{50} for GHRP-2 will enable PD and PK evaluations of extravascular dosing regimens for children. (*J Clin Endocrinol Metab* **83:** 1168–1172, 1998)

THE GH-RELEASING peptides (GHRPs) are a family of molecules that stimulate GH secretion. Originally discovered while searching for a GnRH antagonist, these peptides are structurally related to Met-enkephalin (1–3). Structural modifications have been made to make the GHRPs more effective, selective GH secretagogues. The most potent GHRP to date in humans is GHRP-2 (3, 4). The pharmacology of GHRPs in man has been characterized and well described previously (5–9).

A major potential clinical use for GHRP-2 is stimulation of GH secretion when endogenous secretion is inadequate. In many children with short stature and poor growth rates, the problem appears to be insufficient GH secretion, not an inability to produce GH. Evidence for this includes demonstration of subnormal 12- and 24-h GH pulsatile secretion profiles and a robust GH response when GHRH or GHRP-2 is administered to these children (10–14). Thus, this patient population may potentially benefit from treatment with a GH secretagogue such as GHRP-2.

A feature of the GHRP-2 that makes it an attractive treatment modality resides with its potential for administration by noninvasive methods. Previous investigations have demonstrated release of endogenous GH after the administration of GHRP-2 via the oral, sc, and intranasal routes as well as iv (3, 15–17). This is a possible advantage over GH or GHRH, both of which must be administered parenterally. However, before large scale studies of the safety and efficacy of GHRP-2 can be conducted in children with GH deficiency, the pharmacokinetics (PK) and pharmacodynamics (PD) of this agent in pediatric patients must first be characterized. Therefore, we examined the PK and PD of iv GHRP-2 in children of short stature who were undergoing evaluation for GH deficiency.

Subjects and Methods

This study was of open design, with no blinding of the subjects or investigators. Ten short prepubertal children comprised the study population. These children were all at least 2 SD below the mean height for age, with mean of −3.03 ± 0.16 SD. None of the children had evidence of chronic disease, syndromic disorder, or skeletal dysplasia. The single female patient had a normal karyotype. All children had a slow growth

Received March 7, 1997. Revision received December 30, 1997. Accepted January 12, 1998.

Address all correspondence and requests for reprints to: Catherine Pihoker, M.D., Division of Pediatric Endocrinology, Children's Hospital and Medical Center, P.O. Box 5371, CH-92, Seattle, Washington 98105.

* This work was supported in part by a grant in aid from Wyeth Ayerst Research (Philadelphia, PA) and Grant 1U01-HD-31313–04 (Network of Pediatric Pharmacology Research Units; to G.L.K.) from the NICHHD (Bethesda, MD). Presented in part at the Annual Meeting of the Southern Society for Pediatric Research, New Orleans, LA, February 1, 1996.

rate, delayed bone age, and low serum insulin-like growth factor I levels (Table 1). Responses to GH stimulation tests, using standard secretagogues (*e.g.* arginine, insulin, or L-dopa) were variable, with five patients whose maximal GH response was more than 10 μg/L and five patients whose GH response was less than 10 μg/L. Six of the children (including the five whose maximal GH response was >10 μg/L) had 12-h, overnight GH secretion studies. The mean GH concentration was low in each patient; the group mean was 2.3 μg/L. Magnetic resonance imaging of the head was performed in each child, and no intracranial lesions were observed. Subjects were recruited by informed parental consent and, where appropriate (*i.e.* age ≥7 yr), by patient assent. The protocol was approved by the human research advisory committee of the University of Arkansas for Medical Sciences.

On the day of testing, the subjects arrived at the Day Medicine Unit of Arkansas Children's Hospital between 0700–0800 h after an 8-h fast. There was one exception, that being a child whose testing began at 1300 h after a 4-h fast. An indwelling iv catheter was placed in each subject for the purpose of repeated blood sampling. Two basal (*i.e.* pretreatment) blood samples were obtained at −5 and 0 min for quantitation of both GHRP and GH. A single injection of GHRP-2 (1 μg/kg) was then administered iv over a 60-s period of infusion. Repeated blood samples (1.0 mL each) were obtained at 5, 10, 20, 30, 45, 60, 75, 90, and 120 min after the end of the GHRP-2 infusion. Blood specimens were collected into nonanticoagulant-containing glass tubes, where they were permitted to clot at room temperature for 40 min. The specimens were then centrifuged at 2500 × *g* and 4 C for 10 min. Serum was separated and immediately frozen at −70 C until analysis.

Quantitation of GH from each serum specimen was performed using a commercial polyclonal RIA (Corning-Nichols Institute, San Juan Capistrano, CA). All GH samples from a given subject were run in the same assay, thereby minimizing the effect of interassay variability on pharmacokinetic profiles. Intra- and interassay coefficients of variation of this RIA method for GH were 3% and 8%, respectively. GHRP-2 serum concentrations were determined by a RIA developed and validated by Wyeth-Ayerst Research (Princeton, NJ), which used a polyclonal antibody provided by Dr. C. Y. Bowers. The calibration curve had a range of 62.5–2000 pg/mL. The interassay coefficients of variation and relative errors ranged from 5.8–8.4% and −4.4 to −7.4%, respectively. The GHRP-2 standards, quality control samples, and study samples were analyzed in triplicate, and the mean values were used in performing calculations.

Individual serum concentration *vs.* time data for both GH and GHRP-2 were evaluated in each subject by use of the Siphar/Base software package (SIPHAR, version 4.0, SIMED, Creteil-Cedex, France). Initial polyexponential parameter estimates were generated with a peeling algorithm (18). Final parameter estimates were obtained from curve fitting of individual datasets using a nonlinear, weighted, least squares algorithm, with the weight set as the reciprocal of the calculated plasma concentration (19). Compartment model selection was made after application of the Akaike information criterion (20). Additionally, goodness of fit for the serum concentration *vs.* time data was evaluated by assessment of the variance-covariance matrixes and the coefficients of variation for each polyexponential parameter (*e.g.* coefficients and exponents) calculated from a given model. Finally, model-dependent pharmacokinetic parameters were calculated for both GH and GHRP-2 according to previously described methods (21).

The pharmacodynamics of GHRP-2 were examined by normalization of the posttreatment serum GH values to the mean of two pretreatment measurements to obtain the discrete value of ΔGH. For the pharmacodynamic analysis, the ΔGH values were used as a surrogate biomarker for the pharmacodynamic effect exerted by GHRP-2 in each subject. Visual inspection of the serum concentration *vs.* time data for both GHRP-2 and GH (Fig. 1) and also of the ΔGH *vs.* time values (data not shown) revealed a discordance in the serum concentration profiles compatible with an apparent equilibration delay between the serum concentrations of GHRP-2 and its pharmacological effect, as reflected by serum GH concentrations. Thus, the data suggested that a pharmacokinetic-pharmacodynamic model could be constructed that links the concentration of drug in the central (*i.e.* serum) compartment with the concentration of drug in an effect compartment (22). Accordingly, concentration *vs.* effect profiles were then generated from the ΔGH values for each subject by use of the sigmoid maximal effect model described by Holford and Sheiner (22). Pharmacodynamic parameter estimates [maximal effect (E_{max}) serum concentration associated with 50% response as measured by post-treatment increase in serum concentration (EC_{50}), and sigmoidicity constant (γ)] were then calculated using an extended least squares algorithm with variance assumed to be constant (*i.e.* a homoscedastic model). The pharmacodynamic analysis was conducted using programs contained within the Siphar/D software package (SIPHAR, version 4.0, SIMED).

Serum GH and GHRP-2 concentration data as well as the pharmacokinetic and pharmacodynamic parameter estimates are represented as the mean, SD, and range for the respective values. Relationships between subject age and the pharmacokinetic parameters for the entire study cohort were examined using a nonlinear, least squares, regression algorithm. All statistical tests were performed using subroutines contained within the S-STAT program (SIPHAR, version 4.0, SIMED) or in Excel (version 5.0, Microsoft Corp.). The level of significance accepted for all statistical analyses was $\alpha = 0.05$.

TABLE 1. Initial GH evaluation for short children in study

Subject no.	Age (yr)	Sex	IGF-I	Maximum GH
1	6	F	49	10.1
2	11	M	160	6.9
3	12	M	129	7.1
4	5	M	34	6.6
5	6	M	24	17
6	4	M	37	12
7	8	M	14	8.2
8	6	M	46	9.5
9	7	M	114	14.9
10	8	M	35	15.3

Results

Ten short children received a single iv dose of GHRP-2 and completed the entire study. All subjects tolerated the infusion of GHRP-2 and all study-related procedures without apparent adverse effects. As illustrated in Fig. 1, the mean (±SD) serum GHRP-2 concentration *vs.* time curve revealed a multiphasic relationship that was best fit using a biexponential function. The elimination and distribution rate constants (*i.e.* α and β, respectively) from the curve fit of the

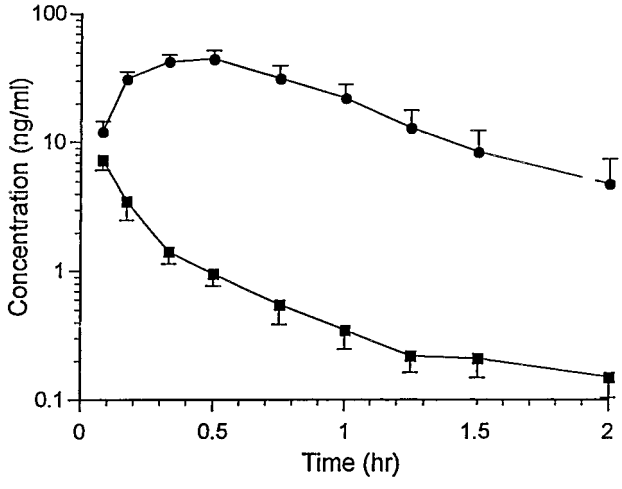

FIG. 1. Serum concentration *vs.* time plot for GHRP-2 (*closed squares*) and GH (*closed circles*) after iv administration of GHRP-2. Data are shown as the mean (±SEM). The generalized serum concentration equation derived from the best fit of the mean data for GHRP-2 was $Cp_t = 1.51 \times e^{-1.32 \times t} + 13.11 \times e^{-10.58 \times t}$, and that for the GH mean data was $Cp_t = 131.62 \times e^{-1.75 \times t} + 158.83 \times e^{-4.97 \times t}$.

mean data were 1.32 and 10.58 h^{-1}, respectively, which yielded the following generalized equation that best described the mean serum *vs.* time concentration profile for GHRP-2: $Cp_{tx} = 1.51 \times e^{-1.32 \times tx} + 13.11 \times e^{-10.58 \times tx}$, where Cp_{tx} represents the plasma concentration of GHRP-2 at any given time point (*i.e.* tx). The excursion of serum concentrations ranged from 7.4 ± 3.8 to 0.15 ± 0.14 ng/mL over a period of 0.083–2.0 h, respectively, after administration of the GHRP-2 dose. A curve fit of the mean serum GHRP-2 *vs.* time data for all subjects revealed a rapid distribution (α) phase with a mean distribution half-life ($t½_\alpha$) of 0.06 h, followed by a longer terminal elimination half-life ($t½_\beta$) with a mean value of 0.52 h.

The polyexponential parameter estimates for GHRP-2 that resulted from the curve fits of the serum concentration *vs.* time data for each subject were used to calculate relevant pharmacokinetic parameters, which are contained and summarized in Table 2. In each instance, a biexponential relationship provided the best fit of the serum concentration data.

The mean (±SD) serum GH concentration *vs.* time data (Fig. 1) also revealed a multiphasic relationship that was best fit using a biexponential function. The appearance and elimination rate constants (*i.e.* K_{app} and K_{el}, respectively) from the curve fit of the mean serum concentration *vs.* time data were 4.97 and 1.75 h^{-1}, respectively, which yielded the following generalized equation that best described the mean serum concentration *vs.* time concentration profile for GH: $Cp_{tx} = 131.62 \times e^{-1.75 \times tx} + 158.83 \times e^{-4.97 \times tx}$, where Cp_{tx} represents the plasma concentration of GH at any given time point (*i.e.* tx). The apparent peak serum GH concentration from these data was 44.8 ± 19.0 ng/mL. Serum GH concentrations declined in an apparent monoexponential fashion after the attainment of the peak concentration (*i.e.* T_{max}) at approximately 0.5 h and declined to 4.8 ± 7.8 ng/mL 2 h after GHRP-2 administration. The curve fit of these data (Fig. 1) revealed a mean first order appearance rate constant (K_{app}) of 4.97 h^{-1} with a corresponding mean appearance $t_{1/2}$ of 0.14 h, and a mean apparent elimination rate constant (K_e) of 0.39 h^{-1} with a corresponding elimination $t_{1/2}$ of 0.4 h.

Pharmacokinetic parameters for GH were calculated using the polyexponential parameters resulting from the curve fits of serum concentration *vs.* time data in each subject and are contained and summarized in Table 3. As was true for the analysis of GHRP-2 data, a biexponential relationship provided the best fit of the serum GH concentration *vs.* time data for each subject (Fig. 1). Three of the 10 subjects did not have quantifiable serum GH concentrations at the 2 h posttreatment collection point. This did not influence the determination of the pharmacokinetic parameters for these subjects, as each of them had a sufficient number of serum concentration *vs.* time points in the elimination phase to produce a reliable estimate of the apparent terminal elimination rate constant.

Examination of the pharmacokinetic parameters for both GHRP-2 and GH (Tables 2 and 3, respectively) for apparent developmental dependence through attempts to correlate them with patient age revealed no statistically significant linear or nonlinear relationships. These same findings were apparent when the pharmacodynamic parameters for GHRP-2 (Table 4) were examined.

For each subject, the plot of the GHRP-2 serum concentration *vs.* effect (*i.e.* ΔGH_t) data produced a counterclockwise hysteresis loop, which was consistent with an equilibration delay between the appearance of GHRP-2 in serum and its pharmacological effect (*i.e.* the stimulation of GH release and its appearance in serum). This particular pharmacodynamic relationship was present for all 10 subjects. Consequently, application of the sigmoid E_{max} model enabled calculation of the pharmacodynamic parameters for GHRP-2 using GH as the surrogate marker of its pharmacological activity. These parameters are summarized in Table 4.

Discussion

The pharmacokinetics of GHRP-2 found in our cohort of pediatric patients are similar to those previously reported in healthy adult volunteers after iv administration of the peptide (3). A comparison of the maximum GH response observed after GHRP-2 administration between these two studies revealed similarities in both the magnitude (*i.e.* mean values = 44 μg/L in children *vs.* 55 μg/L in adults) and time of maximal response (*i.e.* average values = 45–60 min for both). The GH responses observed after iv or sc GHRP-2 are also similar to those previously reported after the parenteral administration of GHRP-6, GHRP-1, or GHRH (3, 4, 23, 24).

To our knowledge, our data represent not only the first report of GHRP-2 pharmacokinetics in pediatric patients, but

TABLE 2. Individual pharmacokinetic parameters for GHRP-2 in short children

Subject no.	β (1/h)	α (1/h)	Cmax (ng/mL)	$AUC^{0\rightarrow\infty}$ (ng/mL·hr)	CL (L/h·kg)	VDss (L/kg)
1	1.61	10.48	5.34	1.29	0.78	0.32
2	1.65	37.58	9.43	1.75	0.57	0.25
3	1.39	20.70	11.54	2.87	0.35	0.20
4	1.66	7.59	3.26	0.77	1.29	0.41
5	1.59	15.82	5.53	1.10	0.91	0.38
6	1.34	6.30	6.47	1.75	0.57	0.23
7	0.93	6.87	15.17	5.44	0.18	0.128
8	1.08	7.35	4.68	1.54	0.65	0.43
9	0.87	7.21	3.73	1.14	0.87	0.62
10	1.17	13.98	8.56	2.56	0.39	0.25
Mean SD	1.33 ± 0.30	13.39 ± 9.74	7.37 ± 3.79	2.02 ± 1.37	0.66 ± 0.32	0.32 ± 0.14

β, Terminal elimination rate constant; α, distribution rate constant; Cmax, apparent peak serum concentration; $AUC^{0\rightarrow\infty}$, area under the serum concentration *vs.* time curve from time zero extrapolated to infinity; CL, total serum clearance; VDss, apparent steady state volume of distribution.

TABLE 3. Individual pharmacokinetic parameters for GH in short children after iv administration of GHRP-2

Subject no.	K_{el} (1/h)	K_{app} (1/h)	Tmax (h)	Cmax (ng/mL)	$AUC^{0\rightarrow\infty}$ (ng/mL · h)	MRT (h)
1	1.28	11.55	0.33	40.85	43.24	0.90
2	2.10	4.95	0.33	32.45	28.17	0.73
3	2.04	4.33	0.50	93.41	76.07	0.81
4	3.15	5.78	0.33	37.33	23.95	0.54
5	2.89	3.46	0.50	47.00	37.65	0.69
6	2.04	4.33	0.50	43.85	30.10	0.80
7	1.54	4.95	0.50	50.90	60.53	0.91
8	1.17	1.58	0.75	57.95	102.61	1.52
9	4.62	8.66	0.17	44.34	21.22	0.39
10	1.41	9.90	0.33	58.94	55.71	0.86
Mean SD	2.22 ± 1.07	5.95 ± 3.11	0.42 ± 0.16	50.70 ± 17.17	47.92 ± 26.1	0.82 ± 0.30

K_{el}, Terminal elimination rate constant; K_{app}, appearance rate constant; Tmax, apparent time of peak serum concentration; Cmax, apparent peak serum concentration; $AUC^{0\rightarrow\infty}$, area under the serum concentration *vs.* time curve from time zero extrapolated to infinity; MRT, mean residence time.

TABLE 4. Individual pharmacodynamic parameters for GHRP-2 in short children

Subject no.	Keo (1/h)	E_0 (ng/mL)	Y	EC_{50} (ng/mL)	Emax (ng/mL)
1	1.49	2.35	6.73	0.81	40.07
2	0.26	5.92	27.21	0.97	93.73
3	0.56	7.90	27.09	1.31	105.00
4	1.54	1.30	4.33	0.66	48.00
5	0.61	2.07	7.22	0.64	92.16
6	0.58	6.89	24.13	0.76	54.70
7	1.10	9.34	12.76	2.39	40.18
8	0.39	18.05	12.03	0.41	72.40
9	3.47	4.71	4.21	1.24	55.40
10	1.32	7.81	5.75	1.71	73.6
Mean SD	1.13 ± 0.94	6.63 ± 4.86	13.15 ± 9.44	1.09 ± 0.59	67.52 ± 23.46

Keo, First order effect equilibrium rate constant; E_0, serum GH concentration associated with no effect from GHRP-2; Y, slope factor of sigmoidicity for concentration *vs.* effect relationship; EC_{50}, serum GHRP-2 concentration associated with 50% response as measured by posttreatment increase in serum GH concentrations; Emax, maximum attainable serum GH concentration after GHRP-2 administration derived from the pharmacokinetic-pharmacodynamic link model.

also the first pharmacodynamic assessment of this peptide. Comparison of the serum concentration *vs.* time profiles for both GHRP-2 and GH in our subjects reveals an equilibration delay in the attainment of peak GH response, a period that we believe corresponds to the time course of GHRP-2 action. This assertion is supported in part by the consistent observation of an equilibration delay between the serum concentrations of GHRP-2 *vs.* effect (*i.e.* ΔGH_t) curves, reflected by the production of a counterclockwise hysteresis and our success in using the sigmoid E_{max} model to effectively determine the pharmacodynamic parameters for GHRP-2. As previously reported by Holdford and Sheiner (22), the successful application of this pharmacodynamic model suggests both linearity and predictability in the drug concentration *vs.* effect relationship. Given the fact that GH is a proximate biological marker of GHRP (and presumably, GHRP-2) activity (23, 24), our assumptions entailed in the pharmacodynamic analysis of our data appear valid and reflective of the expected pharmacological response of GHRP-2.

Despite the apparent differences in serum GH pharmacokinetics reported after exogenous administration of the hormone (25) as opposed to the administration of GH secretagogues (26–30), both the pharmacokinetic and pharmacodynamic data from our study can be used to address the potential therapeutic efficacy of GHRP-2 in pediatric patients with GH insufficiency. First, the mean AUC for GH after the iv administration of a single 1 μg/kg dose of GHRP-2 (*i.e.* 50.7 ng/mL·h) was approximately 50% of the AUC at steady state (*i.e.* 114.2 ± 32.7 ng/mL·h) previously reported in a study of pediatric patients who received daily sc doses of 43 μg/kg methionyl GH (25). If one assumes linearity in the dose-response relationship for iv GHRP-2, administration of a single 2 μg/kg iv dose would be expected to produce an AUC for GH that would be virtually identical to that observed under steady state conditions after sc administration of the currently recommended daily doses of recombinant human GH (25), doses that have been shown to produce acceptable rates of linear growth in children who are GH deficient (30). Second, both the C_{max} (mean, 50.7 ng/mL) and E_{max} values for GHRP-2 in our patient cohort (mean GH, 67.5 ng/mL) actually exceeded the average C_{max} values for GH (37.6 ± 11.6 ng/mL; range, 17.6–49.5 ng/mL) after a single sc dose of 0.1 mg/kg methionyl GH to GH-deficient children (25). Finally, the EC_{50} for GHRP-2 in our study cohort (1.1 ± 0.6 ng/mL) was substantially less than the C_{max} value (7.4 ± 3.8 ng/mL). This particular finding not only supports the adequacy of the 1 μg/kg iv dose of GHRP-2 in producing a desirable biological effect, but also suggests that extravascular administration of this peptide by a route that could be associated with up to a 50% reduction in bioavailability may still produce an acceptable increase in the serum GH concentration sufficient to initiate and sustain a desired growth response. This hypothesis is being tested by our group in

dose-ranging studies of oral and intranasal GHRP-2 that are currently underway.

In conclusion, both the pharmacokinetics and pharmacodynamics of iv administered GHRP-2 in short children are predictable and reflective of the potential for therapeutic application of this peptide. The data produced in this investigation will enable the selection of GHRP-2 doses for future evaluation of their bioavailability, safety, tolerance, and efficacy in children.

Acknowledgments

The authors gratefully acknowledge the analytical support provided by Drs. Ronald Jordan and Boas Gonen from Wyeth Ayerst Research, and the clinical contributions of Nancy Lowery, R.N., C.C.R.C., in the conduct of this investigation.

References

1. **Bowers CY, Momany FA, Reynolds GA, Hong A.** 1984 On the *in vitro* and *in vivo* activity of a new synthetic hexapeptide that acts on the pituitary to specifically release GH. Endocrinology. 114:1537–1545.
2. **Bowers CY, Sartor AD, Reynolds GA, Badger TM.** 1991 On the actions of the growth hormone-releasing hexapeptide, GHRP. Endocrinology. 128:2027–2035.
3. **Bowers CY.** 1993 GH releasing peptides–structure and kinetics. J Pediatr Endocrinol. 6:21–31.
4. **Bowers CY, Veeraragavan K, Sethumadhavan.** 1994 Atypical growth hormone releasing peptides. In: Bercu BB, Walker RF, eds. Growth hormone. II. Basic and clinical aspects. New York: Springer-Verlag; 203–222.
5. **Mericq V, Cassorla F, Garcia H, Avila A, Bowers CY, Merriam GR.** 1995 GH responses to GHRP and to GHRH in GH deficient children. J Clin Endocrinol Metab. 80:1681–1684.
6. **DeBell WK, Pezzoli SS, Thorner MO.** 1991 GH secretion during continuous infusion of GHRP: partial response attenuation. J Clin Endocrinol Metab. 72:1312–1316.
7. **Bowers CY, Alster DK, Frentz JM.** 1992 The growth hormone releasing activity of synthetic hexapeptide in normal men and short statured children after oral administration. J Clin Endocrinol Metab. 74:292–298.
8. **Bercu BB, Yang S, Masuda R, Walker RF.** 1992 Role of selected endogenous peptides in GHRP activity: analysis of GHRH, thyroid hormone releasing hormone, and gonadotropin-releasing hormone. Endocrinology. 130:2579–2586.
9. **Saggese G, Cesaretti G, Giannessi N, Bracaloni C, Cinquanta L, Cioni C.** 1992 Stimulated GH secretion in children with delays in pubertal development before and after the onset of puberty: relationship with peripheral plasma GH-releasing hormone and somatostatin. J Clin Endocrinol Metab. 74:272–278.
10. **Bercu BB, Shulman D, Root AW, Spiliotis BE.** 1986 Growth hormone provocative testing frequently does not reflect endogenous GH secretion. J Clin Endocrinol Metab. 63:709–716.
11. **Goji K.** 1993 Pulsatile characteristics of spontaneous GH concentration profiles in boys evaluated by an ultrasensitive immunoradiometric assay: evidence for ultradian periodicity of GH secretion. J Clin Endocrinol Metab. 76:667–670.
12. **Martin JB, Reichlin SY.** 1987 Clinical neuroendocrinology. New York: Springer Verlag; 51.
13. **Gelato MC, Malozowski S, Caruso-Nicoletti M, et al.** 1986 GH responses to GHRH during pubertal development in normal boys and girls: comparison to idiopathic short stature and GH deficiency. J Clin Endocrinol Metab. 63:174–179.
14. **Pihoker C, Middleton R, Bowers CY.** 1995 Diagnostic studies with intravenous and intranasal GHRP-2 in children of short stature. J Clin Endocrinol Metab. 80:2987–2992.
15. **Mericq V, Cassorla F, Salazar T, et al.** Increased growth velocity during prolonged GHRP-2 administration to GH deficient children [Abstract]. Proc of the 77th Annual Meet of The Endocrine Soc. 1995; 85.
16. **Pihoker C, Bowers CY, Middleton R, Reynolds GA, Badger TM.** Treatment effects of intranasal GHRP-2 in GH deficient children [Abstract]. Proc of the 77th Annual Meet of The Endocrine Soc. 1995; 504.
17. **Laron Z, Frenkl J, Eshet R, Klinger B, Silbergeld A.** Human GH and insulin-like growth factor-1 stimulating and growth promoting effects by long term intranasal administration of the hexapeptide-hexarelin [Abstract]. Proc of the 77th Annual Meet of The Endocrine Soc. 1995; 504.
18. **Gomeni R, Gomeni C.** 1979 AUTOMOD: a polyalgorithm for an integrated analysis of linear pharmacokinetic models. Comput Biol Med. 9:38–48.
19. **Marquardt DW.** 1963 An algorithm for least-squares estimation of nonlinear parameters. J Soc Indust Appl Mathemat. 11:431–441.
20. **Yamaoka K, Nakagawa T, Uno T.** 1978 Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm. 6:165–175.
21. **Wagner JG.** 1976 Linear pharmacokinetic equations allowing direct calculation of needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J Pharmacokinet Biopharm. 4:443–467.
22. **Holford NHG, Sheiner LB.** 1981 Understanding the dose-effect relationship: clinical applications of the pharmacokinetic-pharmacodynamic model. Clin Pharmacokinet. 6:429–453.
23. **Evans WS, Vance ML, Daiser DL, et al.** 1985 Effects of intravenous, subcutaneous, and intranasal administration of GHRH-40 on serum GH concentrations in normal men. J Clin Endocrinol Metab. 61:846–850.
24. **Wilton P, Chardet Y, Danielson K, Widlund L, Gunnarsson R.** 1993 Pharmacokinetics of GHRH(1–29)-NH_2 and stimulation of GH secretion in healthy subjects after intravenous or intranasal administration. Acta Paediatr. 288(Suppl):10–15.
25. **Kearns GL, Kemp SF, Frindik JP.** 1991 Single and multiple dose pharmacokinetics of methionyl GH in children with idiopathic GH deficiency. J Clin Endocrinol Metab. 72:1148–1156.
26. **Parker ML, Vtiger RD, Daughaday WH.** 1962 Studies on human growth hormone. II. The physiological disposition and metabolic fate of human growth hormone in man. J Clin Invest. 41:262–268.
27. **Refetoff S, Sonksen PH.** 1970 Disappearance rate of endogenous and exogenous human growth hormone in man. J Clin Endocrinol Metab. 30:386–392.
28. **Usala AL, Blumer JL.** 1989 Pharmacology of new hormonal therapies in the treatment of pediatric endocrine disorders. Pediatr Clin North Am. 36:1157–1182.
29. **Skamene A, Patel YC.** 1984 Infusion of graded concentrations of somatostatin in man: pharmacokinetics and differential inhibitory effects on pituitary and islet hormones. Clin Endocrinol (Oxf). 20:555–564.
30. **Kemp SF, Kearns GL, Frindik JP.** 1993 Clinical and biochemical correlates of growth associated with short term administration of methionyl growth hormone. Dev Pharmacol Ther. 20:199–204.