# Pharmacokinetic-Pharmacodynamic Modeling of Ipamorelin, a Growth Hormone Releasing Peptide, in Human Volunteers

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*Received March 29, 1999; accepted June 6, 1999*

***Purpose.*** To examine the pharmacokinetics (PK) and pharmacodynamics (PD) of ipamorelin, a growth hormone (GH) releasing peptide, in healthy volunteers.

***Methods.*** A trial was conducted with a dose escalation design comprising 5 different infusion rates (4.21, 14.02, 42.13, 84.27 and 140.45 nmol/kg over 15 minutes) with eight healthy male subjects at each dose level. Concentrations of ipamorelin and growth hormone were measured.

***Results.*** The PK parameters showed dose-proportionality, with a short terminal half-life of 2 hours, a clearance of 0.078 L/h/kg and a volume of distribution at steady-state of 0.22 L/kg. The time course of GH stimulation by ipamorelin showed a single episode of GH release with a peak at 0.67 hours and an exponential decline to negligible GH concentration at all doses. The ipamorelin–GH concentration relationship was characterized using an indirect response model and population fitting. The model employed a zero-order GH release rate over a finite duration of time to describe the episodic release of GH. Ipamorelin induces the release of GH at all dose levels with the concentration ($SC_{50}$) required for half-maximal GH stimulation of 214 nmol/L and a maximal GH production rate of 694 mIU/L/h. The inter-individual variability of the PD parameters was larger than that of the PK parameters.

***Conclusions.*** The proposed PK/PD model provides a useful characterization of ipamorelin disposition and GH responses across a range of doses.

**KEY WORDS:** ipamorelin; growth hormone releasing peptide (GHRP); population pharmacokinetics/pharmacodynamics; indirect response model.

## INTRODUCTION

Human growth hormone (hGH) has been used for the last four decades to treat children with short stature due to growth hormone (GH) insufficiency (1–3). Besides its role in growth, GH is one of the most important metabolic hormones with anabolic as well as catabolic actions (2). One of the major drawbacks that considerably limits the expansion of clinical use of hGH has been the need for daily intramuscular or subcutaneous injections of the drug, resulting in poor patient compliance (3). Furthermore, GH deficiency has been attributed in many cases to defects in pituitary hormone synthesis rather than to hormone secretion (4). Alternatively, growth hormone releasing peptides (GHRP) are being investigated for GH-replacement therapy (5,6). These GHRP are proposed to stimulate the GH production by acting at both the pituitary and hypothalamus regions (7). Also, it is known that GHRP elicit their pharmacological effect synergistically with GH-releasing hormone (8).

Ipamorelin has been chosen for development as a non-invasive growth hormone releasing substance. However in the present study a formulation intended for intravenous administration has been used to characterise the pharmacokinetics and pharmacodynamics of ipamorelin. The objective of the current report is to develop an integrated pharmacokinetic (PK)–pharmacodynamic (PD) model to describe the stimulation of GH production by ipamorelin given as an intravenous infusion over a range of doses to healthy male subjects.

## METHODS

### Subjects

Forty-eight healthy, non-smoking, male subjects with a mean age of 31 years (range: 25–41 years) and a mean weight of 77 kg (range: 59–100 kg) were enrolled in the trial. Subjects with insulin like growth factor-1 (IGF-1) concentrations out of normal range, history of drug sensitivity, allergy, recent history of alcohol abuse, or any subjects who were considered otherwise unsuitable by the investigator were not included in the study. The trial was performed in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. All subjects provided written informed consent prior to participating in the trial.

### Trial Design

This trial was a randomised, placebo-controlled, dose escalation study in which five groups of healthy male subjects received either a 15 min intravenous infusion of ipamorelin (6 subjects/group) or a placebo (2 subjects/group). The doses investigated were: 4.21, 14.04, 42.13, 84.27, and 140.45 nmol/kg. Blood samples were obtained at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 105 minutes and 2, 3, 4, 6, 8 and 10 hours after dosing to determine the plasma ipamorelin and GH concentrations. Additional samples were collected at 12, 14, 16 and 24 hours after dosing for the two larger dose groups.

### Analytical Methods

A solid-phase extraction and reversed phase high performance liquid chromatographic assay with gradient elution method was employed to quantify plasma ipamorelin concentrations as described previously (9). The limit of quantitation (LOQ) was 4 nmol/L (2.8 μg/L). Plasma concentrations of GH were determined using an immunoradiometric kit (Immunotech, Westbrook, Maine). The assay is a sandwich-type assay using two different mouse monoclonal antibodies directed against the GH molecule.

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### Pharmacokinetic Analysis

Plasma ipamorelin concentration–time profiles were described using a two-compartment model:

$$\frac{dA_p}{dt} = \frac{Dose}{T_{inf}} - k_{10} \cdot A_p - k_{12} \cdot A_p + k_{21} \cdot A_t,$$

(if $t > T_{inf}$ then Dose = 0) (1a)

$$\frac{dA_t}{dt} = k_{12} \cdot A_p - k_{21} \cdot A_t \quad (1b)$$

where $T_{inf}$ is the duration of the zero-order ipamorelin infusion rate, $k_{10}$ is the first-order elimination rate constant, $k_{12}$ and $k_{21}$ are the first-order transfer rate constants between the plasma and tissue compartments, and $A_p$ and $A_t$ are the amounts of drug in the plasma and tissue compartments. The model was reparameterized in terms of the systemic clearance (CL), intercompartmental clearance ($CL_d$), volumes of distribution of the plasma ($V_c$) and tissue ($V_t$) compartments. In the subjects who showed peak ipamorelin concentrations later than 15 min, $T_{inf}$ was fixed at the observed peak time. The inter-individual variability (IIV) of each PK parameter was described using a log-normal variance model. A combined proportional and additive error model was used to describe the residual variability. Data from all doses were fitted simultaneously using NONMEM (10).

The areas under the ipamorelin concentration-time curves (AUC), determined using the trapezoid method, were fitted to Eq. (2) to evaluate dose-proportionality.

$$AUC = \alpha \cdot Dose^{\beta} \quad (2)$$

where $\alpha$ and $\beta$ are coefficients estimated using nonlinear regression.

### Pharmacodynamic Analysis

The GH-releasing hormone (GHRH) and somatostatin regulate the synthesis and release of GH from somatotrophs. It was postulated that GHRP act at both the hypothalamus and pituitary levels in synergy with GHRH (7). Somatostatin inhibits the secretion of GH. Indirect response models assume that the drug elicits its action either by stimulating or inhibiting the production or dissipation of a pharmacological response (11). Ipamorelin was hypothesized to stimulate the secretion of GH in an 'episodic' manner, i.e., for a finite duration of time, according to Eq. 3a and 3b.

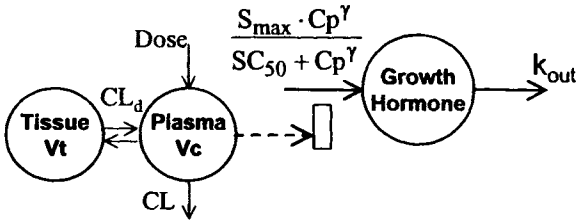


**Fig. 1.** Models used to describe the pharmacokinetics (two-compartment model) and pharmacodynamics (indirect response model) of ipamorelin. See text for explanation of terms.

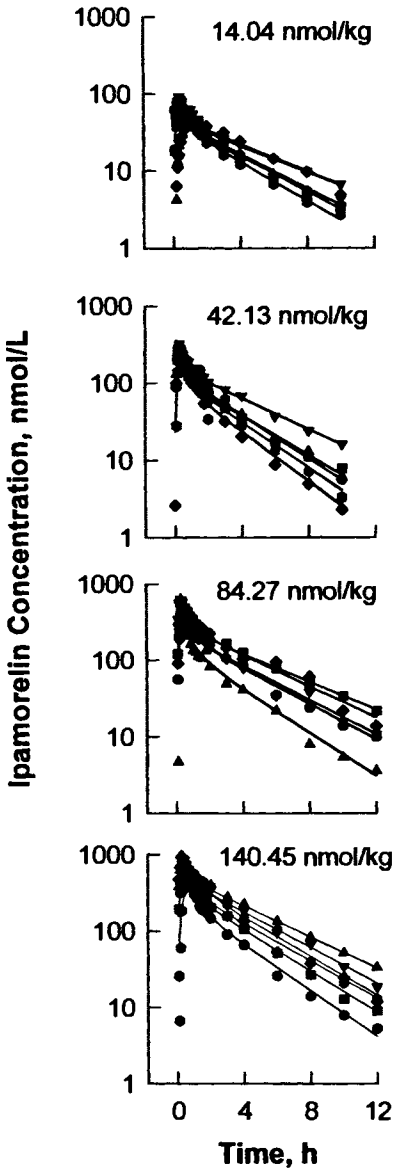


**Fig. 2.** Plasma ipamorelin concentration versus time profiles after infusion of 14.02, 42.13, 84.27, and 140.45 nmol/kg doses in healthy subjects. The symbols are the observed data and lines indicate the individual (posthoc) predictions.

$$\frac{dC_{GH}}{dt} = \left[\frac{S_{max} \cdot C_p^{\gamma}}{SC^{\gamma 50} + C_p^{\gamma}}\right] - k_{out} \cdot C_{GH} \quad (\text{if } t \le T_{GH}) \quad (3a)$$

$$\frac{dC_{GH}}{dt} = -k_{out} \cdot C_{GH} \quad (\text{if } t > T_{GH}) \quad (3b)$$

where $S_{max}$ is the maximum rate of release of GH, $SC_{50}$ is the concentration of peptide required for half-maximal stimulation of GH, $C_p$ is the plasma peptide concentration predicted by Eq. 1, $k_{out}$ is the GH elimination rate constant, $C_{GH}$ is the plasma GH concentration, $\gamma$ is the sigmoidicity factor, and $T_{GH}$ is the duration of GH release.

The IIV of each of the PD parameters was described using a log-normal variance model. A combined proportional and additive error model was used to describe the residual variability. The GH levels of the placebo and 4.21 nmol/kg dose groups

were negligible and were not included in the pharmacodynamic analysis. Data from all other doses were fitted simultaneously using the NONMEM software (10).

## RESULTS

### Pharmacokinetic Analysis

Figure 2 shows the observed and fitted plasma concentration-time profiles in 12 individual healthy subjects given 14.02, 42.13, 84.27, or 140.45 nmol/kg of ipamorelin as an intravenous infusion over 15 min. Data from all doses were fitted simultaneously. Post-infusion ipamorelin concentrations decline in a bi-exponential fashion with a terminal half-life of about 1 h. The PK parameters for the two-compartment model (CL, $V_c$, $CL_d$, and $V_t$) and the estimated IIV are shown in Table 1. The population and individual (posthoc) pharmacokinetic predictions are shown in Fig. 3. Dose-proportionality analysis of AUC resulted in a power coefficient (β) of 0.99 indicating linearity within the dose range investigated.

### Pharmacodynamic Analysis

The simultaneous fittings for individual subjects using the indirect response model at four different doses are shown in Fig. 4. The GH concentrations rise to a sharp peak at around 0.67 h and decline to very low concentrations at all doses by 6 h, mimicking a typical response to a short duration zero-order infusion. The peak GH levels occurred later than the ipamorelin peak concentrations indicating a delay in eliciting the pharmacological effect. However the plasma ipamorelin concentrations persisted for a longer duration than the GH concentrations. The maximum GH concentrations attained in the 84.27 and 140.45 nmol/kg ipamorelin dose groups were similar. The placebo (mean = 1.31 mIU/L) and 4.21 nmol/kg (mean = 6.31 mIU/L) dose groups showed negligible and erratic GH levels, while the mean GH concentration for the 140.45 nmol/kg dose group was 80 mIU/L. Hence, the placebo and lowest dose groups were not used in the analysis.

The population parameters and the IIV derived using the IRM are presented in Table I. The population and individual (posthoc) predictions of drug and GH concentrations are shown in Fig. 3. Plots of the individual pharmacodynamic parameters and covariates (age, body weight) did not demonstrate any trends.

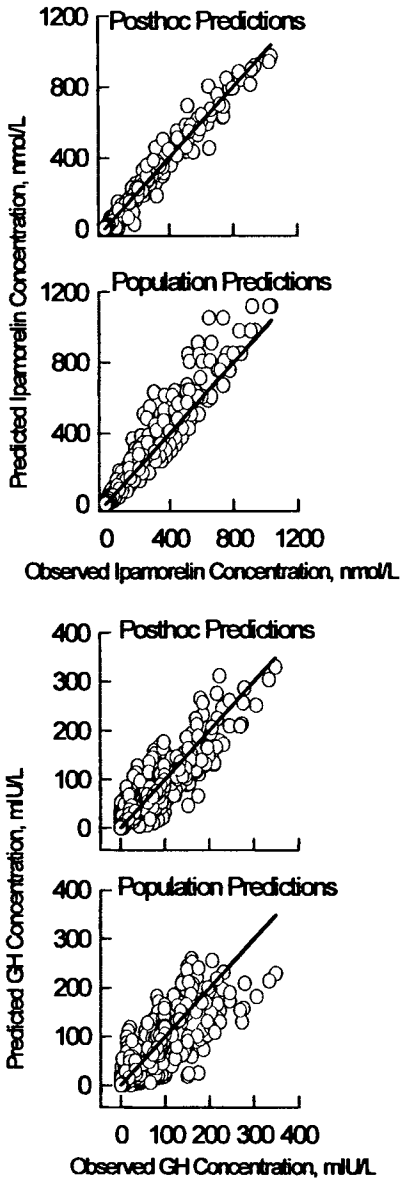


**Fig. 3.** Population and individual (posthoc) predictions of ipamorelin and growth hormone concentrations. The lines indicate identity.

**Table 1.** Summary of Population Pharmacokinetic and Pharmacodynamic Parameters (± SE) of Ipamorelin in Healthy Subjects.

| | Pharmacokinetics | | | |
|---|---|---|---|---|
| | CL, L/h/kg | $V_c$, L/kg | $CL_d$, L/h/kg | $V_t$, L/kg |
| Mean | 0.078 (0.007) | 0.102 (0.024) | 0.107 (0.021) | 0.119 (0.009) |
| CV (%) | 28 | 37 | 9 | 13 |

| | Pharmacodynamics Indirect Response Model | | | | |
|---|---|---|---|---|---|
| | $k_{out}$, $h^{-1}$ | $T_{GH}$, h | $S_{max}$, mIU/L/h | $SC_{50}$, nmol/L | γ |
| Mean | 0.72 (0.019) | 0.67 ($5 \times 10^{-5}$) | 694 (298) | 214 (91) | 2.02 (0.28) |
| CV (%) | 42 | 22 | 33 | 130 | 101 |

*Note:* The inter-individual variability is presented as the coefficient of variation (CV).

## DISCUSSION

### Pharmacokinetic Analysis

Ipamorelin exhibits linear pharmacokinetics well described by a two-compartment model (Fig. 2). This GH-releasing peptide has a short terminal half-life of about 2 h with a systemic clearance of 0.078 L/h/kg and a steady-state volume of distribution ($V_{ss}$) of 0. 22 L/kg in a typical subject. A large molecule such as a peptide is primarily localized in the central compartment and thus a small $V_{ss}$ is expected. Experiments in male rats (9) yielded a similar $V_s$ (0.2 L/kg), faster

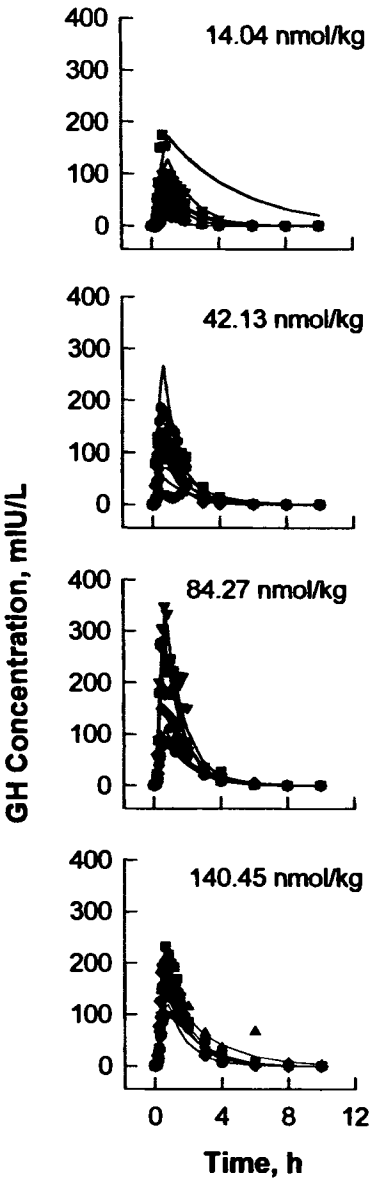


**Fig. 4.** Plasma GH concentration versus time profiles, fitted using the indirect response model (Eqs. 3a & 3b), after infusion of 14.02, 42.13, 84.27, and 140.45 nmol/kg doses of ipamorelin in healthy subjects. The symbols are the observed data and lines indicate the individual (posthoc) predictions.

clearance (0.3 L/h/kg) and hence a shorter terminal half-life (0.5 h). Previous studies on a different peptide, GHRP-2, in short prepubertal children also produced a small $V_{ss}$ (0.32 L/kg) and a half-life of 1.5 h (12).

The coefficient of variation (CV) of the inter-individual errors for CL and $V_c$ were 28% and 37%. The IIV on the peripheral distribution parameters were small (CV ~ 10%). The population and individual posthoc predictions (for all data) are distributed around the line of identity. As expected the individual predictions are more tightly scattered around the observed concentrations. The covariates of age and body weight did not demonstrate any obvious influence on the PK parameters. This may be due to the fact that the study was conducted in healthy male subjects. Studies in patients with more diversity may allow more meaningful examination of covariate influences on the PK parameters.

## Pharmacodynamic Analysis

A semi-parametric pharmacodynamic model to characterise the stimulation of GH by ipamorelin was recently reported (13). The authors employed a linear pharmacodynamic model to describe the stimulation of GH release dependent on the concentration of ipamorelin and an empirical GH-antagonist mechanism attributed to somatostatin. Since each subject was fitted individually in that report, the strength of the proposed model across the dose range is not clear. Previously, a link model was used to describe the pharmacodynamics of a single intravenous dose of GHRP-2 in prepubertal children (12), but this model is physiologically unrealistic for an endogenous substance.

The present model (Eq. 3a, 3b) characterised the effect of ipamorelin on GH release satisfactorily (Fig. 4). This model differs from the basic indirect pharmacodynamic models proposed earlier (11) in two aspects: the present model has no basal response and the response formation rate is only for a finite duration of time.

Many reports indicate that GH is released in a pulsatile or episodic fashion and not in a continuous manner (14,15). The present model reflects this physiological release pattern of GH by using a zero-order release rate over a finite time period ($T_{GH}$). The maximum rate of GH release was 694 mIU/L/h over a release 'episode' lasting for 0.67 h. It is not clear why there is no production or release of GH for a longer duration with higher doses of the peptide (Fig. 4). Studies in normal men infused with a different GHRP (SK&F 110679) over 2 h demonstrated a burst release of GH between 10–70 min followed by smaller episodic secretions (15).

The model predicted maximum plasma GH concentration is about 465 mIU/L (= 694 mIU/L/h·0.67 h) or 2.2 ng/mL/kg in a typical subject which is in accordance with values in swines (1.5 ng/mL/kg) (17). The $SC_{50}$ of ipamorelin to stimulate GH secretion from rat pituitary cells in vitro was 1.3 nmol/L (16). The dose required for half-maximal GH stimulation ($SD_{50}$) in female swines 3 nmol/kg) (17) is not comparable to that in humans (~42 nmol/kg from Fig. 4) and male rats (80 nmol/kg) (17). The $SD_{50}$ can also be determined by multiplying the value of $SC_{50}$ and $V_{ss}$ (46 nmol/kg). There seems to be dissimilar $SD_{50}$ values of ipamorelin in rats and swines even for other GH-releasing peptides. For example, the $SD_{50}$ of GHRP-6 in rats is 30 nmol/kg while that in swines is 0.6 nmol/kg (17).

Doses higher than 42.13 nmol/kg will produce plasma ipamorelin concentrations higher than the $SC_{50}$ (232 nmol/L). The model described in this study and in previous reports (15) suggests that prolonged exposure to GHRP concentrations may not necessarily produce the usually expected stimulation for longer periods. The necessity to include the sigmoidicity factor ($\gamma$) in the pharmacodynamic model reflects a steep concentration-effect relationship. This may influence the response to GHRP treatment and provide a reason to develop non-invasive GHRP formulations. Missing ipamorelin doses (non-compliance) may result in abrupt decreases in GH stimulation.

The coefficient of variation of the inter-individual errors on the pharmacodynamic parameters range from 20 ($T_{GH}$) to 130% ($SC_{50}$). None of this variability could be explained by

the covariates such as age and body weight. The apparent elimination half-life of GH is about 0.9 h (= $0.693/k_{out}$) which is slightly larger than the half-life of endogenous GH (about 0.5 h) in healthy human subjects (14). However, a wide range for the endogenous GH half-life (10 to 50 min) was reported (15).

The mechanism of GH regulation in the body is complex and may not be completely understood. Most assumptions in the present model are inferences from the response profiles and current understanding of GH regulation. The weaknesses of the model are the use of an 'episodic' GH release phenomenon, which will not allow the extrapolation of results to other dosing regimens. However, this was necessitated by the obviously brief period of secretion. Studies with more informative dosing strategies and quantitation of other endogenous substances like GH-releasing hormone and somatostatin will allow confirmation and elaboration (with respect to the homeostatic control of GH) of the model structure. Nevertheless, the model presented in the current report appears to characterize satisfactorily the ipamorelin-GH concentration relationship at all doses.

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