Kinetic Analysis of the Disposition of Insulin-Like Growth Factor 1 in Healthy Volunteers

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Purpose. Insulin-like growth factor 1 (IGF-1) is predominantly bound to its specific binding proteins (IGFBPs) in circulating plasma. In the present study, pharmacokinetic analysis of IGF-1 was performed in healthy volunteers to characterize the effect of interactions with IGFBPs on IGF-1 disposition.

Methods. Plasma concentration profiles of both free and bound IGF-1 were examined at several doses. An *in vitro* plasma protein binding was also analyzed.

Results. The total body clearance (CL_{total}) for the free IGF-1 was much higher than the creatinine clearance, suggesting that the major elimination pathway is by a route other than renal glomerular filtration. The CL_{total} for the free IGF-1 exhibited a dose-dependent reduction whereas that for the sum of unbound and bound IGF-1 increased on increasing the dose. The data obtained fitted closely a one-compartment model that involved the binding and dissociation of IGF-1, as well as its biosynthesis and elimination. The estimated parameters suggest that IGF-1 exhibits high affinity binding to IGFBPs, the rate-limiting step in the overall elimination being the dissociation from IGFBPs.

Conclusions. The saturation of both the plasma protein binding and elimination accounts for the nonlinear pharmacokinetic profile. The binding to IGFBPs markedly limits both the distribution and elimination of IGF-1.

KEY WORDS: IGF-1; IGFBP; pharmacokinetics; healthy volunteers.

INTRODUCTION

Insulin-like growth factor 1 (IGF-1) is a polypeptide with a molecular weight of 7.6 kDa. IGF-1 is a pleiotropic growth factor with a variety of pharmacologic effects, including the ability to promote of glucose uptake in peripheral tissues, reduce plasma free fatty acids, and exert a significant growth-promoting action (1,2). IGF-1 is synthesized and secreted mainly in the liver, and its gene transcription is primarily regulated by growth hormone (GH). Thus, IGF-1 is considered to mediate the biologic action of GH. Its exogenous administration markedly stimulates physical growth, especially in growth hormone resistance syndrome.

Unlike many other cytokines, IGF-1 in circulating plasma is bound predominantly to its specific binding proteins (IGFBPs). IGFBPs are categorized into two groups as far as their affinity for IGFs is concerned, high-affinity (IGFBPs1-6) and low-affinity (IGFBPs7 and 8) genes (3). Among these, IGFBP3 is a major determinant of the circulating levels of IGF-1 in plasma and it forms a 150 kDa tertiary complex with both IGF-1 and an acid-labile subunit (4,5). Considering the great difference in the molecular size of unbound (free) and bound IGF-1, it is reasonable to suppose that its pharmacokinetics could be significantly affected by such plasma protein binding.

The pharmacokinetics of IGF-1 has been analyzed both in animals (6,7) and humans, including healthy volunteers and patients with growth hormone receptor deficiency, those undergoing peritoneal dialysis or suffering from chronic renal failure, and those with partial IGF-1 gene deletion (8–11). To obtain further information on its disposition characteristics in humans, we performed a kinetic analysis of the plasma disappearance of free and bound IGF-1 at several doses based on simple mathematical modeling techniques (Fig. 1). Recently, Boroujerdi *et al.* (5,12) established a pharmacokinetic model for IGF-1 that involves the binding of IGF-1 to IGFBPs in circulating plasma, passage of only free IGF-1 across the capillary endothelial barriers, and its receptor binding in peripheral tissues. In the present study, we attempted to establish a simpler model that can fully describe IGF-1 kinetics in humans because of the limited amount of actual data available for fitting to the more complex model. Blum (13) proposed a one-compartment model taking into account biosynthesis, IGFBP binding, and elimination of IGF-1. However, this model was applied only to endogenous levels, and the parameters for the latter two factors were held constant. In the present study, we examined the disposition of free and bound IGF-1 in healthy volunteers. The profiles obtained can be fitted to the one-compartment model, giving us information on the kinetics of the plasma protein binding, distribution, and elimination of free and bound IGF-1.

MATERIALS AND METHODS

Volunteers and Study Design

Forty-two healthy male volunteers were recruited for this study. The study protocol was approved by the Institutional Review Board of Kyushu Clinical Pharmacology Research Clinic. Informed consent was obtained from all volunteers. Volunteers were assigned to six treatment groups. Each group consisted of five subjects given IGF-1 and two subjects given physiologic saline. The volunteers given physiologic saline were omitted from the pharmacokinetic analysis. The characteristics of volunteers given IGF-1 are listed in Table I. Each treatment group received 5, 10, or 20 μg/h/kg by intravenous (i.v.) infusion for 3 h, 20 μg/h/kg by i.v. infusion for 6 hours, or 60 or 120 μg/kg by subcutaneous (s.c.) bolus injection. Recombinant human IGF-1 was supplied by Genentech, Inc. (South San Francisco, CA). Before administration and at designated times thereafter, serial blood samples were collected. EDTA plasma was harvested after centrifugation at approximately 1800g × 20 min and stored at –20°C until IGF-1 determination was performed.

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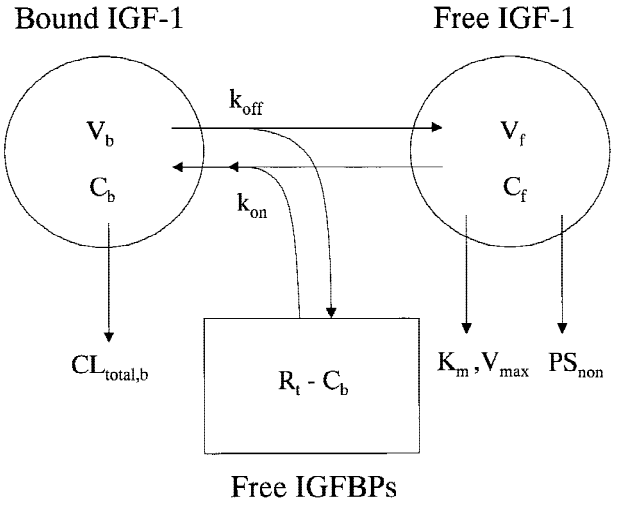

Fig. 1. Pharmacokinetic model describing the plasma concentration profiles of free and bound IGF-1 in humans.

Assays

The plasma concentration of IGF-1 was measured by conventional radioimmunoassay (RIA). The presence of serum binding proteins interferes with the RIA of IGF-1. Therefore, the total plasma concentration of IGF-1 was measured by RIA after separation from binding proteins by acid/ethanol extraction (14,15). The recovery of IGF-1 in the RIA method after acid/ethanol extraction ranged from 100 to 116%. The extracts were neutralized, appropriately diluted, and subjected to RIA. Free IGF-1 was separated by high-performance gel filtration chromatography using a TSK gel G2000SW column (Toso, Tokyo). The separated free IGF-1 fractions were measured by RIA. Anti rhIGF-1 polyclonal rabbit antiserum was provided by Genentech, Inc. ^{125}I-labeled IGF-1 was purchased from Amersham (Buckinghamshire, UK). The detection limits for total and free IGF-1 were 10 and 0.5 ng/mL, respectively. The intra- and inter-assay variation (C.V.) in total IGF-1 was less than 10.2 and 10.8%, respectively. The intra- and inter-assay variation (C.V.) in free IGF-1 was less than 18.0 and 13.2%, respectively. Plasma and urine creatinine was determined by the Jaffe method (16).

In Vitro Plasma Protein Binding

IGF-1 was dissolved in phosphate buffer (pH 7.4) containing 0.025% Tween 20 and diluted with pooled blank human plasma to a final IGF-1 concentration of 3 to 50 nM. After a 1-h incubation at 37°C, an aliquot of the incubation mixture was collected, and free IGF-1 was determined as described above. A pilot experiment was carried to check that the plasma protein binding of IGF-1 reached a steady state after the 1-h incubation (data not shown). The concentrations of bound IGF-1 (C_b) were calculated by subtracting the measured free IGF-1 concentration (C_f) from the total IGF-1

Table I. Characteristics and Pharmacokinetic Parameters in Healthy Volunteers

	Intravenous infusion				Subcutaneous injection	
	15 μg/kg/3 hr	30 μg/kg/3 h	60 μg/kg/3 h	120 μg/kg/6 h	60 μg/kg	120 μg/kg
Volunteers						
Age (years)	22.0 ± 1.9	20.6 ± 0.5	23.4 ± 1.7	21.2 ± 0.8	22.8 ± 2.2	22.4 ± 1.1
BW (kg)	64.5 ± 3.7	63.0 ± 3.5	63.1 ± 7.4	60.0 ± 4.1	61.1 ± 3.0	68.1 ± 4.3
Ccr (mg/dL)	0.82 ± 0.08	0.90 ± 0.19	0.98 ± 0.08	1.00 ± 0.07	0.92 ± 0.13	0.94 ± 0.09
CLcr (mL/h/kg)	NE[a]	NE[a]	NE[a]	NE[a]	115 ± 11	107 ± 10
Total IGF-1						
C_0 (ng/mL)	181 ± 59	208 ± 51	178 ± 52	189 ± 36	195 ± 26	171 ± 50
T_{max} (h)	NA[b]	NA[b]	NA[b]	NA[b]	4.2 ± 1.1	4.8 ± 1.8
C_{max} (ng/mL)	319 ± 65	483 ± 127	472 ± 63	684 ± 104	428 ± 34	525 ± 52
ΔC_{max} (mg/mL)	138 ± 20	275 ± 80	294 ± 114	495 ± 74	233 ± 19	354 ± 23
ΔAUC (ng · h/mL)	2006 ± 658	3028 ± 694	3960 ± 1295	6809 ± 887	4233 ± 473	5689 ± 556
CL_{total} (mL/h/kg)	8.1 ± 2.6	10.3 ± 2.3	16.3 ± 4.6	17.9 ± 2.2	14.3 ± 1.8[e]	21.3 ± 2.1[e]
$T_{1/2}$ (h)	31.2[c]	35.0[c]	24.1[c]	30.7[c]	28.7 ± 6.9	22.2 ± 3.1
Free IGF-1						
C_0 (ng/mL)	1.7 ± 1.6	1.1 ± 1.5	<QL[d]	<QL[d]	3.2 ± 0.5	2.4 ± 0.5
T_{max} (h)	NA[b]	NA[b]	NA[b]	NA[b]	1.8 ± 0.4	2.0 ± 0.0
C_{max} (ng/mL)	14.4 ± 3.5	23.8 ± 6.7	61.4 ± 16.1	81.9 ± 10.3	53.9 ± 11.2	98.9 ± 18.0
ΔC_{max} (ng/mL)	12.7 ± 2.2	22.7 ± 7.1	61.4 ± 16.1	81.9 ± 10.3	50.7 ± 11.0	96.5 ± 18.2
ΔAUC (ng · h/mL)	32.5 ± 3.9	65.4 ± 12.8	175.1 ± 60.6	504.7 ± 64.0	183.5 ± 31.2	455.6 ± 50.6
CL_{total} (mL/h/kg)	468 ± 58	475 ± 106	385 ± 154	240 ± 27	334 ± 56[e]	266 ± 28[e]
$T_{1/2}$ (h)	0.59 ± 0.14	0.50 ± 0.26	0.34 ± 0.06	0.34 ± 0.05	1.77 ± 0.41	2.14 ± 0.31

Note. Data are expressed as mean ± SD of five volunteers. C_0, endogenous (predose) concentration; C_{max}, maximum concentration; ΔC_{max}, C_{max} above the endogenous level calculated as "$C_{max} - C_0$"; ΔAUC, area under the curve above the endogenous level; CL_{total}, total body clearance calculated as dose/ΔAUC; $T_{1/2}$, elimination half-life.

[a] Not examined.

[b] Not applicable.

[c] Determined from the mean concentration of five subjects.

[d] Below quantitation limit.

[e] Assuming that the bioavailability is unity based on kinetic analysis (Table II).

concentration, which was the sum of the measured endogenous total IGF-1 and added IGF-1. The data obtained for free and bound IGF-1 were fitted to Eq (1) by the WinNonLin program (Scientific Consulting, Inc.).

$$C_b = R_t*C_f/(K_d + C_f) \quad (1)$$

where K_d and R_f are the equilibrium dissociation constant and maximum binding capacity of IGF-1, respectively.

Model-Independent Analysis

The endogenous IGF-1 level (C_o), which was determined in a plasma sample collected just before administration, the maximum concentration of IGF-1 after administration (C_{max}) and the time of C_{max} (T_{max}) were the observed values. To calculate the exogenous IGF-1 concentration, assuming the endogenous IGF-1 level was not changed by administration of IGF-1, the C_0 was subtracted from each measured concentration. The C_{max} for exogenous IGF-1 (ΔC_{max}) was calculated as $C_{max} - C_0$. The area under the concentration-time curve for exogenous IGF-1 (ΔAUC) was calculated by the trapezoidal rule up to 24 h after administration. The total body clearance ($C_{total}L$) of free or total IGF-1 was calculated as Dose/ΔAUC. The elimination half-life of IGF-1 was estimated from the apparent rate constant (k) as ln2/k. The creatinine clearance that followed s.c. administration was determined as the ratio of the amount excreted into urine, from 12 h before to 24 h after the s.c. injection, to the AUC of creatinine during the same period.

Model-Dependent Analysis

Bound IGF-1 was calculated by subtracting free IGF-1 from total IGF-1. The plasma concentration of free (C_f) and bound (C_b) IGF-1 during intravenous infusion was fitted to Eqs (2) and (3), respectively.

$$V_f(dC_f/dt) = -k_{on}(R_t - C_b)*C_f*V_b + k_{off}*C_b*V_b - [PS_{non} + V_{max}/(K_m + C_f)]*C_f + V_{syn} + Inf \quad (2)$$

$$V_b(dC_b/dt) = k_{on}(R_t - C_b)*C_f*V_b - k_{off}*C_b*V_b - CL_{total,b}*C_b \quad (3)$$

where V_f, V_b, PS_{non}, V_{max}, K_m, V_{syn}, Inf, and $CL_{total,b}$ are the distribution volume for free IGF-1, the distribution volume for bound IGF-1, the non-saturable clearance for IGF-1, the maximum velocity of saturable elimination, the Michaelis constant for saturable elimination, the synthesis rate of endogenous IGF-1, the infusion rate, and the total clearance for bound IGF-1, respectively. Because we assumed that V_{syn} is not affected by IGF-1 infusion, V_{syn} can be estimated as:

$$V_{syn} = [PS_{non} + V_{max}/(K_m + C_{o,f})]*C_{o,f} \quad (4)$$

where $C_{0,f}$ is the endogenous free IGF-1 concentration, taken as the mean value of five volunteers in each treatment group (Table I). The plasma concentration of free and bound IGF-1 after the end of intravenous infusion was fitted to Eqs (2) and (3), respectively, whereas in Eq. (2) the last term on the right-hand side of the equation (+Inf) has been deleted. After subcutaneous injection, the plasma concentration of free and bound IGF-1 after intravenous infusion was fitted to Eqs (5) and (3), respectively:

$$V_f(dC_f/dt) = -k_{on}(R_t - C_b)*C_f*V_b + k_{off}*C_b*V_b - [PS_{non} + V_{max}/(K_m + C_f)]*C_f + V_{syn} + k_a*F*\exp(-k_a*t) \quad (5)$$

where k_a and F are the absorption rate constant and the bioavailability, respectively. Simultaneous fitting was performed using all the data from the intravenous infusion of four doses and two doses after s.c. injection using an iterative nonlinear least-squares method with a Napp program (17). The input data were weighted as the reciprocal of the square of the observed values and the algorithm used for the fitting was the Damping Gauss Newton Method. Initial values of fitted parameters were estimated as follows: F was estimated from the ratio of the AUC after sc injection to that after i.v. injection; K_m was estimated as the dissociation constant of IGF-1 from its receptor (18) ; V_{max} was estimated from K_m, PS_{non}, and CL_{total} of free IGF-1 after i.v. infusion at 15 μg/kg/3h. The initial value of $CL_{total,b}$ was varied from ×1 to ×1/1000 of the clearance for free IGF-1 ($PS_{non} + V_{max}/K_m$). V_f and V_b were estimated as the extracellular volume and the plasma volume (19), respectively.

RESULTS

Disposition Profile of IGF-1

To analyze the plasma protein binding, distribution, and elimination of IGF-1 in humans, IGF-1 was infused i.v. or injected s.c. into healthy male volunteers and both the free and total IGF-1 in plasma were determined. The pharmacokinetic parameters estimated by model-independent analysis are listed in Table I. The time- courses of free and bound IGF-1 are illustrated in Figs. 2 and 3. The endogenous total and free IGF-1 did not change following administration of physiologic saline (Fig. 2E). During infusion, both the free and bound IGF-1 concentrations increased, and the former increased more rapidly than the latter (Fig. 2). After the end of infusion, the plasma free IGF-1 fell rapidly whereas the reduction in bound IGF-1 was not so obvious (Fig. 2). After s.c. injection, free IGF-1 also increased rapidly, followed by a decrease, whereas the bound IGF-1 concentration changed relatively slowly (Fig. 3). In this case the disappearance of free IGF-1 was relatively slow (Fig. 3A) compared with that after intravenous administration (Fig. 2A). In both the i.v. infusion and sc injection studies, the CL_{total} for total IGF-1 increased on increasing the dose (Table I). However, the CL_{total} for free IGF-1 decreased in a dose-dependent manner (Table I).

To examine the contribution of the glomerular filtration rate (GFR) to the overall elimination of IGF-1, we calculated the CL_{cr} and compared it with the CL_{total} for free IGF-1. The plasma creatinine levels of all volunteers were within the normal range (Table I). The CL_{cr} estimated for s.c. administration did not vary as much, 115 ± 11 mL/h/kg for the 60 μg/kg group and 107 ± 10 mL/h/kg for the 120 μg/kg group, whereas a relatively large inter-individual variability was found in the CL_{total} for free IGF-1 within each dose group (Table I). The mean $CL_{total}$of each dose group ranged from 240 to 475 mL/h/kg and was at least twice as great as the CL_{cr}.

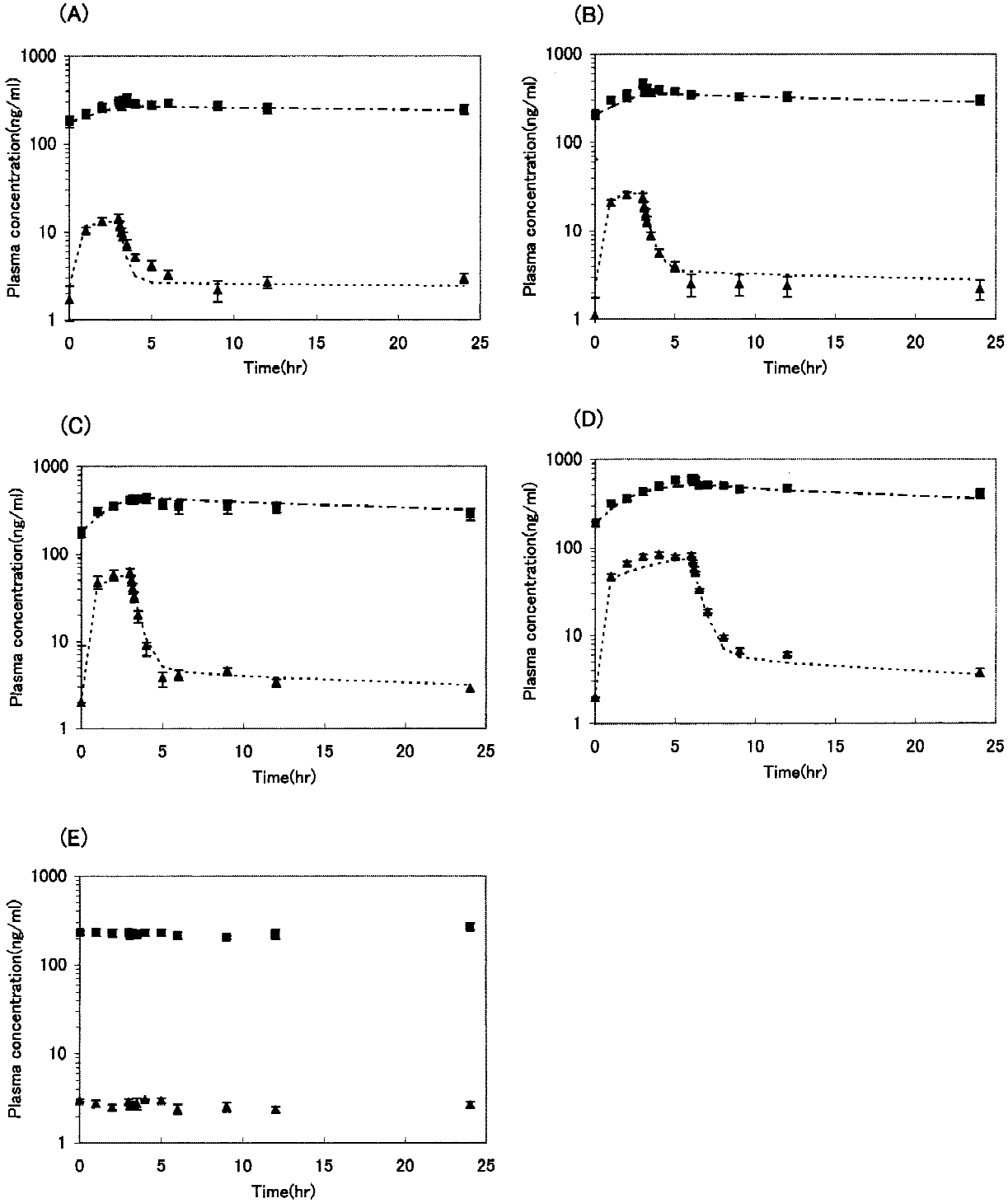

Fig. 2. Plasma concentration of free (▲) and bound (■) IGF-1 after intravenous infusion. Male volunteers received an intravenous infusion of 15 (A), 30 (B), and 60 (C) μg IGF-1/3h/kg, 120 μg IGF-1/6h/kg (D), and saline (E). The free and total plasma IGF-1 concentrations were determined and bound IGF-1 was calculated. Data represent mean ± SE of five volunteers. The solid line represents the fitted line based on the mathematical model shown in Fig. 1.

Estimation of Pharmacokinetic Parameters

To characterize the kinetics of IGF-1 disposition, a mathematical model-dependent analysis was performed based on the one-compartment model described in Fig. 1. To increase the accuracy of the parameters, all the data for the plasma concentrations at several doses were simultaneously fitted to Eqs (2) to (5) to estimate the parameters (Table II). The fitted lines could basically be superimposed on the actual data for each injection route (Figs. 2 and 3). The obtained value for F was close to unity (Table II), which was compatible with a previously reported finding (9). The estimated $CL_{total,b}$ was much smaller than the elimination clearance for free IGF-1 (V_{max}/K_m+PS_{non}) (Table II). Although the absolute value of

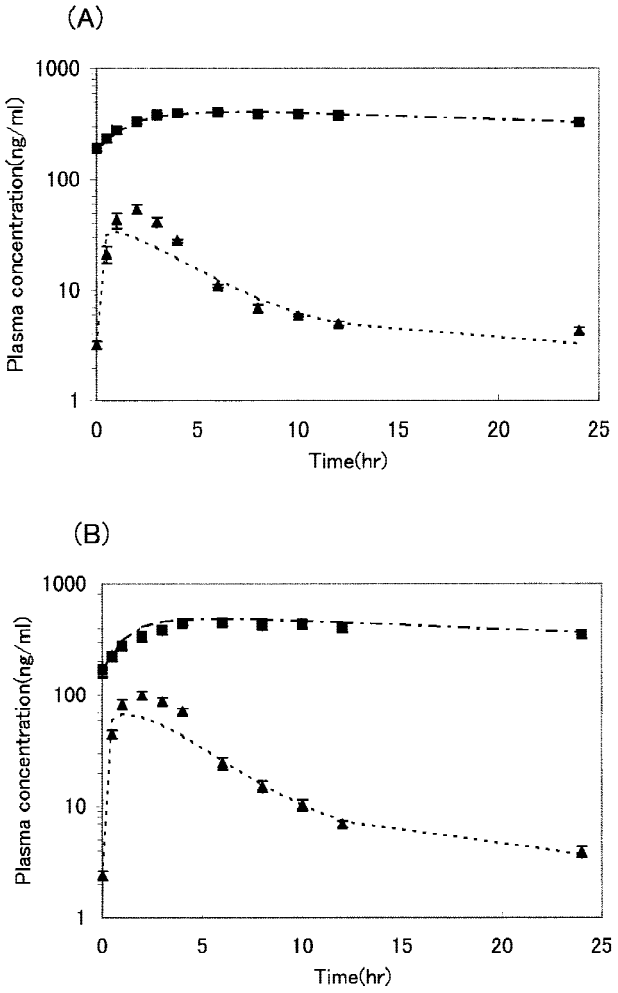

Fig. 3. Plasma concentration of free (▲) and bound (■) IGF-1after subcutaneous injection. Male volunteers received a subcutaneous bolus injection of IGF-1 at 60 (A) and 120 (B) μg/kg. Free and total plasma IGF-1 concentrations were determined and bound IGF-1 was calculated. Data represent mean ± SE of five volunteers. The solid line represents the fitted line based on the mathematical model shown in Fig. 1.

Table II. Pharmacokinetic Parameters Estimated for IGF-1 Disposition in Healthy Volunteers[a]

V_f (mL/kg)	168 ± 15
V_b (mL/kg)	54.8 ± 10.3
k_{on} (ng/mL/h)	0.00971 ± 0.00143
k_{off} (h^{-1})	0.0409 ± 0.0079
K_D (ng/mL)	4.21[b]
R_t (ng/mL)	542 ± 29
PS_{non} (ml/h/kg)	111[c]
K_m (ng/mL)	90.5 ± 38.1
V_{max} (ng/h/kg)	$2.53 \times 10^4 \pm 0.59 \times 10^4$
$CL_{total,b}$ (mL/h/kg)	$1.81 \times 10^{-10} \pm 6.29 \times 10^{-3}$
k_a (h^{-1})	0.310 ± 0.020
F	1[d]

[a] Data represent mean ± calculated SD.
[b] Calculated as k_{off}/k_{on}.
[c] In terms of the mean measured creatinine clearance for volunteers receiving a subcutaneous injection.
[e] This parameter was calculated to be 1.05 ± 0.06 and was greater than 1.

the $CL_{total,b}$was not very reliable because of its large calculated SD, such a calculated SD value was also much smaller than the clearance (V_{max}/K_m+PS_{non}) for free IGF-1 clearance, suggesting that the $CL_{total,b}$ could be considered to be negligible.

Plasma Protein Binding Examined *In Vitro*

To verify the binding parameters obtained *in vivo,* the plasma protein binding of IGF-1 was also examined *in vitro* under equilibrium conditions. The data obtained were fitted to the Langmuir-type equation, Eq (1). The estimated K_d and R_t were 4.75 ng/mL (0.6 nM) and 253 ng/mL (33 nM), i.e., there was no more than a two-fold difference compared with the values found *in vivo* (Table II).

DISCUSSION

In the present study, we analyzed the disposition of IGF-1 in humans based on a kinetic model (Fig. 1). Although this model was a simple one, describing only one site for plasma protein binding, one compartment each for free and bound IGF-1, and two types (linear and nonlinear) of elimination route, the actual data generally fit this model (Figs. 2 and 3). Considering the variety of pharmacologic activities exhibited by IGF-1, care needs to be taken to keep its clinical plasma concentration steady. Therefore, the present analysis may be a suitable means of monitoring IGF-1 concentrations. The two- to three-fold difference between V_f and V_b suggests that free IGF-1 can be distributed into a larger space than the IGF-1 bound to IGFBPs. Because the V_b is almost exactly the same as the plasma volume (approximately 40 mL/kg body wt) (19), IGFBPs limit the distribution of IGF-1 and retain it within the circulating plasma. The maximum binding capacity for IGF-1 (R_t), estimated as 548 ng/mL (72 nM), was close to the plasma IGFBP3 concentration in healthy men (70–140 nM) (5). This may be reasonable when we consider that the major form of IGF-1 in plasma is the 150 kDa ternary complex with IGFBP3 and an acid-labile subunit, which is too large to easily penetrate the capillary endothelial cells in most organs. Exogenously administered IGF-1 forms not only such a 150 kDa complex, but also a 50 kDa complex that is assumed to bind to IGFBP1 (20). Therefore, incorporation of two binding sites into kinetic models may be physiologically preferable, like the models reported by Boroujerdi *et al.* (5,12). However, the plasma IGFBP1 level (1–15 nM) is much lower than that of IGFBP3 (5), and so our model with only one binding site may be sufficient in practical terms to describe the plasma concentration-time profile.

The present analysis also suggests that IGFBPs limit the elimination of IGF-1 from the circulation. The elimination half-life of free IGF-1 ranged from 0.34 to 0.59 h after i.v. infusion (Table I), indicating its rapid elimination, whereas the dissociation half-life ($ln2/k_{off}$) for bound IGF-1 was 17 h (Table II). Although the elimination clearance of bound IGF-1 ($CL_{total,b}$) was included in our model, the estimated $CL_{total,b}$was much smaller than the elimination clearance of free IGF-1 ($V_{max}/K_m + PS_{non}$) (Table II). Thus, plasma protein binding results in marked retention of IGF-1 by avoiding its rapid elimination and the rate-limiting step of IGF-1 elimination is its dissociation from IGFBPs.

Considering that the molecular weight of free IGF-1 (7.6 kDa) is such that free IGF-1 is able to undergo glomerular filtration in the kidney, we compared the $CL_{total}$for free IGF-1 with CL_{cr} because this comparison will identify the contribution of such filtration to the overall clearance. The CL_{total} for free IGF-1 decreased dose-dependently and was at least two-fold greater than the CL_{cr} (Table I). Therefore, the major clearance mechanism for free IGF-1 is not glomerular filtration. Although the exact elimination mechanism is still unknown, Kimura *et al.* (6) reported the greatest accumulation of ^{125}I-rhIGF-1 in the kidneys and an almost 90% reduction in the total clearance of IGF-1 during renal vasculature ligation in rats. Therefore, it is likely that the kidney is the major organ responsible for IGF-1 clearance. If so, an efficient elimination mechanism should be present on the basolateral side in the kidney because the CL_{total} is much greater than the GFR. With this in mind, two components were considered in the elimination of IGF-1 (Fig. 1). Because the CL_{total} for free IGF-1 exhibited a slight nonlinearity as the dose increased (Table I), one of the components was assumed to be a saturable pathway whereas the PS_{non} was fixed as the mean creatinine clearance, corresponding to the glomerular filtration rate, of all the volunteers (111 mL/h/kg). The K_m in the saturable clearance of free IGF-1 was estimated as 90.5 ng/mL (12 nM). This value was comparable with the dissociation constant (~9 nM) of IGF-1 from its receptors transfected in *Xenopus laevis* oocytes (18), suggesting that the saturable clearance may be governed by receptor-mediated endocytosis which is the major elimination mechanism for certain types of growth factors, such as epidermal growth factor, hepatocyte growth factor, erythropoietin, and granulocyte colony stimulating factor (21–24). Because the IGF-1 receptor is widely expressed in many different organs, including the kidney, receptor-mediated endocytosis in the kidney may be involved in IGF-1 elimination (1,25,26).

The level of IGFBPs in the circulation is known to change in various conditions. For example, plasma IGFBP3 levels are higher in chronic renal failure (18, 27) and lower in growth hormone deficiency (27) or in Laron-type dwarfs (28, 29) than in normal subjects. Because the present analysis was performed in healthy volunteers, the pharmacokinetic parameters obtained in the present study may be different from those in such conditions and further studies are needed to analyze the disposition of IGF-1 in such conditions.

In conclusion, we performed a pharmacokinetic analysis of IGF-1 in human volunteers. This analysis revealed that the overall disposition of IGF-1 can be described by a one-compartment model involving the saturation of both plasma protein binding and elimination. IGFBPs play a key role in keeping free IGF-1 in the circulation by limiting its systemic distribution and elimination.

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