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Pharmacokinetics of insulin-like growth factor-1 in advanced chronic renal failure

RALPH RABKIN, FERNANDO C. FERVENZA, HELEN MAIDMENT, JOHN IKE, RAYMOND HINTZ, FRANCES LIU, DUANE C. BLOEDOW, ANDREW R. HOFFMAN, and NEIL GESUNDHEIT

Department of Medicine and Pediatrics, Stanford University School of Medicine, Department of Medicine, Veterans Affairs Palo Alto Health Care System, Palo Alto, and Genentech, Inc., South San Francisco, California, USA

Pharmacokinetics of insulin-like growth factor-1 in advanced chronic renal failure. Information regarding the impact of chronic renal failure (CRF) on IGF-1 serum clearance is limited. Thus we evaluated the pharmacokinetics of insulin-like growth factor-1 (IGF-1) in six normal adults and six adults with advanced CRF (serum creatinine 7 ± 0.8 mg/dl). All subjects were given 80 μg/kg recombinant human IGF-1 s.c. and blood was sampled over 48 hours. Baseline total serum IGF-1 levels were similar in both groups, but peak levels were elevated significantly in CRF; this was apparently related to the reduced distribution volume in CRF subjects. CRF did not affect the metabolic clearance rate (MCR) of total serum IGF-1. Immunoreactive IGF binding protein-3 (IGFBP-3) levels were greater in CRF. Western immunoblots revealed that the apparent increase in IGFBP-3 was largely due to an increase in immunoreactive fragments. IGFBP-3 protease activity was not increased. Thus IGFBP fragment accumulation likely reflects reduced fragment clearance. Western ligand blots revealed elevated 30 and 34 kDa IGFBP levels and IGFBP products in CRF serum. Serum acid labile subunit levels were unchanged in CRF. Peak free IGF-1 levels and the MCR of free IGF-1 did not differ between groups. In both groups the MCR of free IGF-1 exceeded the MCR of total IGF-1 by approximately 30-fold. These data suggest that in CRF patients receiving s.c. IGF-1: (a) total serum IGF-1 levels are increased as a result of elevated circulating IGFBPs that may restrict the distribution of IGF-1 beyond plasma; (b) serum free IGF-1 levels are not altered; and (c) the IGF-1 MCR is unchanged in CRF. Thus, in advanced CRF, apart from a reduction in the total IGF-1 volume of distribution the pharmacokinetics of IGF-1 are largely unaltered.

Insulin-like growth factor-1 is a 7.6 kD member of the insulin-related peptide family that is produced in tissues throughout the body, especially liver [1]. In the circulation, IGF-1 resides largely bound to circulating high affinity IGF binding proteins (IGFBP) but less than 1% is present as the free uncomplexed hormone [2]. Altogether six IGF binding proteins have been identified. In the circulation IGFBP-3 is by far the most abundant with lesser amounts of IGFBP-1, 2, 4 and -6 present. Usually ~90% of the plasma IGF-1 circulates complexed to both IGFBP-3 (~ 40 to 50 kD depending on glycosylation) and an acid labile subunit (ALS) (~85 kD) forming a 150 kD moiety. A small amount is bound to IGFBP-1, -2, -4 and -6 forming smaller complexes. Because of the size of the IGF-IGFBP complex, it is thought that IGFBPs limit transcapillary passage of IGF-1 resulting in prolongation of the serum clearance of IGF-1. This is especially evident with IGF-1 in the 150 kD moiety. Release of IGF-1 from IGFBP complexes is achieved, in part, by circulating and tissue proteases which lower the affinity of the IGFBP to IGF-1 [3].

Adding further to the complexity of IGF-1 physiology are the wide fluctuations of plasma IGFBP concentrations that occur in response to physiologic and pathologic stimuli. For example, during fasting or pregnancy, plasma intact IGFBP-3 levels fall [3]. In diabetes there is a fall in IGFBP-3 levels while IGFBP-1 levels rise [4], and in chronic renal failure the concentration of several IGFBPs increase [5, 6]. It has been suggested that the increase in plasma IGFBPs in renal failure reduces IGF-1 bioavailability, thereby contributing to the uremia-induced resistance to IGF-1 [7].

In general the kidney is a major site of protein hormone removal, and in renal failure the serum clearance of peptide hormones, including that of insulin and proinsulin, is reduced [8]. Given the profound changes in the serum IGFBP profile that occur in chronic renal failure (CRF) and the loss of the kidney as a source of IGF-1 clearance, we postulated that the pharmacokinetics of IGF-1 will be altered in renal failure. If true this may have important clinical implications since IGF-1 is under evaluation for the treatment of some of the consequences of renal failure [9, 10]. We therefore sought to determine the effect of advanced renal failure on the pharmacokinetics of subcutaneously administered IGF-1.

Methods

We studied six healthy adult males and six adult males with advanced chronic renal failure. All subjects gave their consent under a protocol approved by the Stanford University Medical Center Human Subjects Review Committee. The key characteristics of these volunteers are listed in Table 1. The healthy subjects had no prior history or evidence of renal disease. The entry criteria for the CRF subjects included a serum creatinine above 2.5 mg/dl, freedom from illness for at least three months and no requirement for renal dialysis. Exclusion criteria included serious medical conditions such as malignancy, chronic cardiac, liver or pulmonary disease, collagen vascular disease, insulin requiring diabetes, malnutrition (relative body wt < 80% or > 140% of IBW, serum albumin < 3 g/dl). The cause of renal disease was

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Table 1. Subject characteristics

	Normals ($N = 6$)	Patients ($N = 6$)
Age *years*	43 ± 13	45 ± 3
Weight *kg*	84 ± 7	79 ± 3
BUN *mg/dl*	13 ± 1	67 ± 9[a]
Serum creatinine *mg/dl*	1.1 ± 0.4	7.0 ± 0.3[a]
Creatinine clearance *ml/min/1.73 m²*	87 ± 8.8	18 ± 2.2[a]
Serum albumin *mg/dl*	4.5 ± 0.1	4.6 ± 0.2

Data are mean ± SEM.
[a] $P < 0.01$

glomerulonephritis in four subjects and polycystic kidney disease in two.

The subjects were admitted to the Aging Study Unit at the V.A. Palo Alto Health Care System the day before the pharmacokinetic study. They were placed on a 0.8 to 1.0 g protein/kg and 3 to 4 g salt intake per day and a 24 hours urine collection was obtained. The next morning, an intravenous catheter was placed in an arm vein and baseline blood samples were taken 30 minutes and five minutes prior to injection of IGF-1. Then 80 μg/kg recombinant human IGF-1 (Genentech Inc., South San Francisco, CA, USA) was administered rapidly s.c. in the contralateral triceps area, and the patient ate breakfast. Blood was obtained 15, 30, 45, 60 and 90 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 40 and 48 hours after the injection for measurement of glucose, total and free IGF-1 and IGF binding protein levels. The subjects were allowed free access to snacks and caloric containing fluids and were given regular meals at 12 noon, 6 p.m. and 7 a.m. Blood pressure was monitored every 30 minutes for the first one hour after IGF-1 injection then hourly for the next three hours, and then every six to eight hours.

Radiolabeling of peptides

Serum IGF-1, IGF-2 and non-glycosylated IGFBP-3 were iodinated by the chloramine-T method [11]; covalent tracer of [^{125}I]IGF-2 and IGFBP-3 was prepared and purified as described previously [12]. Recombinant IGF-1 was obtained from Bachem, Inc. (Torrance, CA, USA). Recombinant IGF-2 was provided by Eli Lilly Co. (Indianapolis, IN, USA). Recombinant glycosylated IGFBP-3 was purchased from Upstate Biotechnology Inc. (Lake Placid, NY, USA). Non-glycosylated IGFBP-3 was a gift from Celtrix (Santa Clara, CA, USA).

Radioimmunoassay (RIA)

IGF-1 was measured by RIA after separation from IGFBPs by G-50 chromatography in acid, as previously described [13]. Anti-IGF-1 antiserum (UBK487) was provided by Drs. L.E. Underwood and J.J. Van Wyk (Chapel Hill, NC, USA) through the National Hormone and Pituitary Program. Serum IGFBP-3 levels were measured directly [14] using antiserum against IGFBP-3 developed by Dr. R.G. Rosenfeld [15]. Covalent [^{125}I]IGF-2: IGFBP-3 was employed as the tracer for this assay. Assays for free IGF-1 were carried out with kits provided by Diagnostics Systems Laboratories, Inc. (DSL, Webster, TX, USA). The procedure employs a two-site immunoradiometric assay principle with a minimum detection limit of 0.05 ng/ml [16]. The interassay and intrassay coefficient of variation averages 3.6 and 5.1%, respectively. All samples were analyzed in the same assay.

Western ligand blotting

Three microliters of each serum sample were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under non-reducing conditions. Samples were transferred onto nitrocellulose and probed for IGFBPs with [^{125}I]IGF-1 and -2 as previously described [5, 17].

Western immunoblots

Serum samples were separated by 12% SDS-PAGE under non-reducing conditions and electroblotted onto nitrocellulose [18]. Following blocking for four hours at room temperature with 0.1 M Tris-HCl, 0.15 M NaCl, and 0.1% Tween 20, pH 7.4 (TTBS) with 2% BSA (Sigma Chemical Co., St. Louis, MO, USA), the blot was incubated overnight with anti-IGFBP-3 antibody at 1:1000, or anti-acid labile subunit (ALS) antiserum (DSL) at 1:2000 in TTBS at 4°C. After three 10 minutes washes at room temperature with TTBS, the blot was incubated with horseradish peroxidase linked goat anti-rabbit antibody at 1:10,000 (Amersham, Arlington Heights, IL, USA) for one hour at room temperature. After three washes in TTBS, the blot was exposed for one minute to enhanced chemiluminescence (ECL) reagents (Amersham), drained, wrapped in Saran^{Wrap} wrap, and the antibody-labeled bands were examined by exposure to ECL hyperfilm (Amersham) for 10 to 30 seconds.

IGFBP-3 protease assay

IGFBP-3 specific protease in serum was measured as described by Giudice et al [19]. Two microliters of serum were incubated with 30,000 cpm [^{125}I]IGFBP-3 (non-glycosylated) for four hours at 37°C. Term pregnancy serum was used as a positive control. After separation by 12% SDS-PAGE, intact and fragmented IGFBP-3 tracer were detected by autoradiography.

Pharmacokinetic analysis

Free and total serum IGF-1 concentrations (above baseline) over time for each subject were analyzed by compartmental modeling, and pharmacokinetic parameters describing absorption, distribution, and clearance were calculated by standard methods (PCNONLIN, SCI Software, Lexington, KY, USA). The maximum serum free or total IGF-1 concentrations (C_{max}) and the times of the maximum concentrations (t_{max}) were the observed values. The absorption half-life was calculated from the apparent absorption rate constant:

$$\text{Absorption half-life} = 0.693/\text{absorption rate constant}$$

and the half-life for the disappearance of IGF-1 from the serum was estimated from the rate decline in serum IGF-1 concentrations (k):

$$\text{half-life} = 0.693/k$$

Because the subcutaneous availability of IGF-1 was not determined in this study, distribution volume and serum clearance were not corrected for bioavailability (F). The distribution volume (Vd/F) was a parameter of the compartmental fit. The serum IGF-1 metabolic clearance rate (MCR) was calculated from the area under the serum IGF-1 concentration versus time curve extrapolated to infinity (AUC):

$$\text{MCR} = \text{Dose/AUC}$$

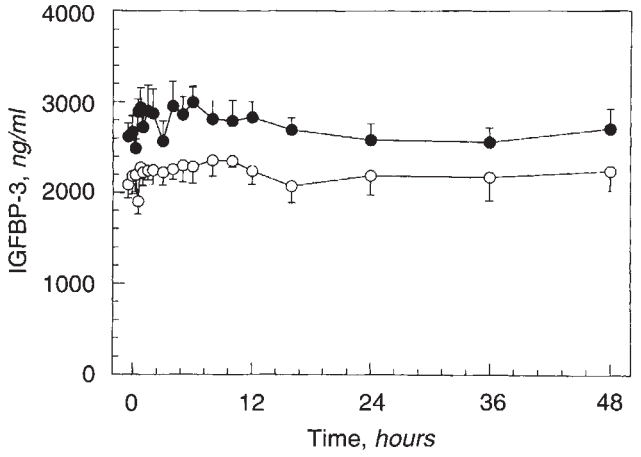

Fig. 1. *Serum immunoreactive IGFBP-3 levels immediately before and after the s.c. injection of IGF-1, 80 μg/kg, in normal ○ and CRF ● subjects.*

The assumed endogenous production rate of IGF-1 was estimated from the serum clearance and baseline total IGF-1 concentration [20]. This estimation assumes that the baseline serum IGF-1 concentration represents the concentration of IGF-1 in serum over the period of study, that the MCR and production rate remain constant after the administration of IGF-1 and finally that there is no synthesis or degradation of IGF-1 in relatively large slow exchange compartments.

Statistical analysis

Values are expressed as the mean ± SEM. Data were analyzed for statistical significance by Student's *t*-test.

Results

Serum IGF binding protein profile

In CRF subjects the serum immunoreactive IGFBP-3 levels were significantly elevated ($P < 0.05$) throughout the study period when compared to the normal controls (Fig. 1). There was no significant change in these levels following the s.c. administration of a single dose of IGF-1. Western ligand analysis, which is dependent on the ability of the IGFBP to bind radioligand, is depicted in Figure 2A. Most conspicuous was a 38 to 42 kDa doublet, the size of IGFBP-3, which was similar in the CRF and control serum. A 34 kDa band consistent with IGFBP-2 and a band at 30 kDa, which could represent IGFBP-1, 5 and perhaps 6, was more prominent in the CRF serum. A 24 kDa band consistent with IGFBP-4 was similar in the two groups. A diffuse signal seen between the 26 to 30 kDa region of the gel probably represents fragmented or deglycosylated IGFBPs. The IGFBP profile did not appear to change following IGF-1 administration.

Western immunoblots were then performed to characterize IGFBP-3 in greater detail (Fig. 2B). The immunoblots revealed that the 38 to 42 kDa doublet is in fact immunoreactive IGFBP-3 and the levels appeared to be similar in the two groups. The antibody also detected a 29 kDa protein which was more conspicuous in the CRF serum. This presumably represents an immunoreactive IGFBP-3 cleavage product. Interestingly, IGFBP-3 protease activity was not increased in the CRF subjects compared to controls. This suggests that the elevated levels of the 29 kDa IGFBP-3 fragment reflects reduced elimination rather than increased production. A representative autoradiogram from a protease assay is depicted in Figure 3. Western immunoblots performed to measure ALS revealed that the levels in CRF serum did not differ significantly from normal control levels (data not shown). IGF-1 administration did not affect serum ALS levels.

Serum total IGF-1 kinetics

The calculated serum total IGF-1 pharmacokinetic parameters are summarized in Table 2 and Figure 4. The change in serum total IGF-1 levels after administration of IGF-1 s.c. is shown in Figure 5. Baseline serum total IGF-1 levels did not differ between CRF and normal subjects (140 ± 8 vs. 130 ± 16 ng/ml). However, maximum serum total IGF-1 levels following s.c. IGF-1 injection were significantly higher in the CRF subjects (720 ± 74 vs. 530 ± 26 ng/ml in controls; $P < 0.05$). The time taken to achieve these peak levels, while on average faster in CRF, did not differ significantly between groups. Of note, the IGF-1 volume of distribution was significantly lower in the CRF group (98 ± 9 vs. 150 ± 20 ml/kg; $P < 0.05$). Since the MCR did not differ significantly between the groups, the increase in maximum serum IGF-1 levels appears to be due to the reduced volume of distribution. Serum total IGF-1 half-life did not differ significantly between the groups. The estimated assumed endogenous IGF-1 production rate was similar in the CRF and control subjects, averaging 29 ± 4 and 38 ± 11 μg/kg/day, respectively.

Serum free IGF-1 kinetics

The serum free IGF-1 time course after s.c. administration of IGF-1 is shown in Figure 6 and the results of the pharmacokinetic analysis is summarized in Figure 4. While the free serum IGF-1 levels were on average higher during the 4 to 16 hours period after the IGF-1 was given, there were no significant differences between the control and CRF subjects in any of the measured serum free IGF-1 parameters. There were, however, major differences between the pharmacokinetics of free IGF-1 and total IGF-1 (Fig. 4). Maximum serum free IGF-1 levels in the two groups (22 ± 2 and 23 ± 1 ng/ml) accounted for less than one tenth of the maximum total serum IGF-1 levels. The MCR of free IGF-1 in normal and CRF subjects (360 ± 73 and 290 ± 65 ml/min/kg) exceeded that of the total IGF-1 MCR (11 ± 0.2 and 10 ± 0.2 ml/min/kg) measured in the same subjects by ~ 30-fold. The volume of distribution of free IGF-1, 3.9 ± 0.82 and 3.0 ± 0.24 liter/kg in normal and CRF subjects, respectively, exceeded the volume of distribution of total IGF-1 by a similar order of magnitude.

Discussion

In this study we observed that following the administration of a single s.c. dose of recombinant human IGF-1, the serum IGF-1 rose to higher maximum levels in subjects with advanced CRF than in normals. Unexpectedly the serum total IGF-1 MCR was unchanged, despite a major loss of renal function. Serum free IGF-1 rose similarly in the two study groups, and again there were no significant group differences between the free IGF-1 MCR or volume of distribution. As anticipated, the volume of distribution and MCR of serum free IGF-1 were considerably greater than the corresponding total IGF-1 parameters. It should be noted that the free IGF-1 assayed likely reflects true free IGF-1 and IGF-1 that rapidly dissociates from IGFBPs (presumably the low molecular

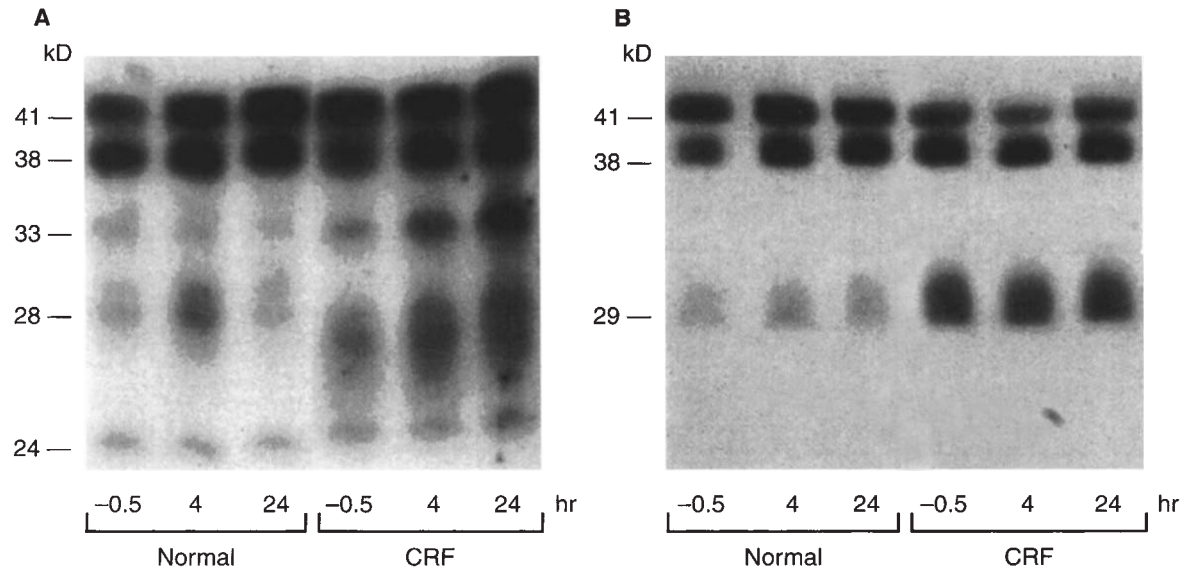

Fig. 2. (**A**) *Western ligand blot of IGFBPs in serum of a normal and CRF subject 0.5 hours before and 4 and 24 hours after the administration of IGF-1 s.c.* (**B**) Western immunoblot with antibody against IGFBP-3 of serum of a normal and CRF subject.

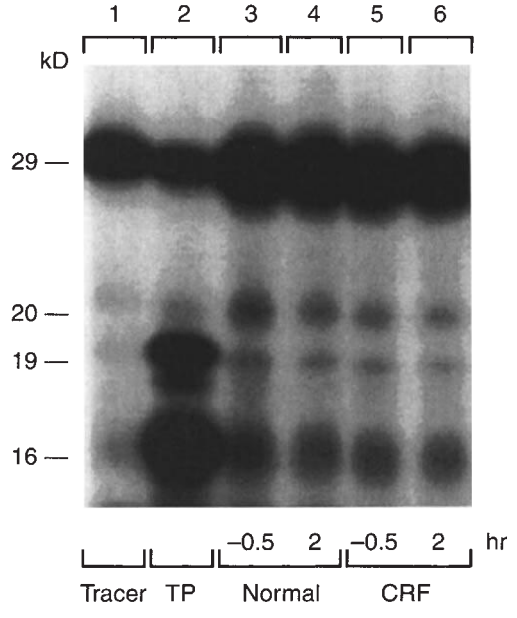

Fig. 3. *IGFBP-3 protease assay.* Pregnancy serum and serum taken from a normal and CRF subject 0.5 hours before and two hours after s.c. IGF-1 administration were incubated with recombinant ^{125}I-IGFBP-3 for four hours. Proteolysis of ^{125}I-IGFBP-3 by pregnancy serum is evident while there is minimal proteolysis in normal and CRF serum.

Table 2. Pharmacokinetic parameters for serum total IGF-1

	Normal (N = 6)	CRF (N = 6)
Baseline serum total IGF-1 *ng/ml*	130 ± 16	140 ± 8
Maximum plasma total IGF-1 (C_{max}) *ng/ml*	530 ± 26	720 ± 74[a]
Time to max serum total IGF-1 (t_{max}) *hr*	5.7 ± 1.1	4.5 ± 0.78
Distribution volume (V/F) *liter/kg*	0.15 ± 0.02	0.098 ± 0.01[a]
Serum clearance (CL/F) *ml/hr/kg*	11 ± 2.0	9.6 ± 1.9
Apparent absorption half-life *hr*	2 ± 0.5	2.1 ± 0.3
Initial half-life *hr*	7 ± 2.0	5.3 ± 1.4
AUC above baseline (*ng/ml*) *hr*	9100 ± 2122	10000 ± 1592

Data are mean ± SEM.
[a] $P < 0.05$

weight moieties) during the assay [16]. In normal subjects the estimated assumed IGF-1 production rate averaged 38 μg/kg/day and was essentially the same as that reported by Wilton et al [20]. The production rate was not significantly different in CRF (29 μg/kg/day).

Profound changes in the serum IGFBP profile were apparent in the CRF subjects that did not change following the single dose of IGF-1. In these subjects, the serum immunoreactive IGFBP-3 levels were significantly elevated. As judged by Western immunoblot, this material consisted of intact IGFBP-3 and a 29 kDa fragment. Both moieties were present in normal serum but only the 29 kDa fragment was elevated in the CRF serum. The serum level of immunoreactive ALS, a glycoprotein that forms a 150 kDa complex with circulating IGF-1 and IGFBP-3, was not elevated. In contrast Western ligand blot analysis revealed an increase in the 30 and 34 kDa IGFBPs, which is consistent with the reported increase in IGFBP-1 and IGFBP-2 in uremia [5, 6]. In addition, there was a diffuse signal in the 26 to 30 kDa region that likely reflects IGFBP fragments and perhaps deglycosylated IGFBPs. Since IGFBPs sequester circulating IGF-1, limiting its passage into the tissues, it is likely that the increase in serum IGFBPs in CRF accounts for the lower total IGF-1 volume of distribution in these subjects. Another likely consequence of IGF-1 trapping by elevated serum IGFBP levels is attenuated bioavailability [2, 21] and this may contribute to the resistance to IGF-1 action seen in uremia [7, 22]. There is, however, preliminary evidence suggesting that skeletal muscle IGF-1 resistance may also be due to a post-receptor signaling defect [23].

Since the levels of free (bioavailable) IGF-1 were similar in

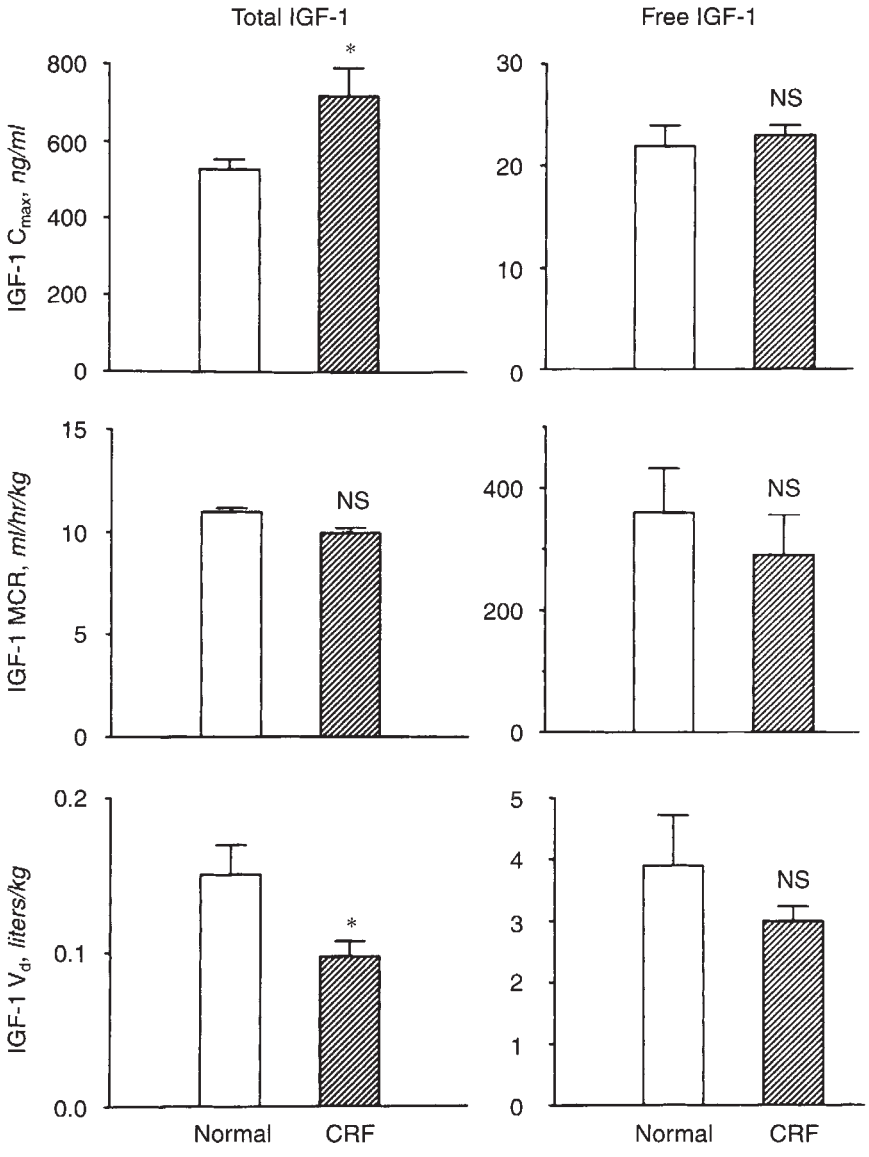

Fig. 4. *Summary of total and free serum IGF-1 maximum levels (C_{max}), metabolic clearance rates and volume of distribution (Vd) measured in normal and CRF subjects following the sc injection of IGF-1 (80 μg/kg).* Note different scales for total and free IGF-1 values.

control and CRF subjects after the acute administration of IGF-1 and as the IGF-1 MCR did not differ between the two groups, it would appear from this pharmacokinetic study that the dose of IGF-1 in CRF, at least in the short term, does not require modification. However, as resistance to the metabolic action of IGF-1 has been noted in patients with end-stage renal disease, the dose of IGF-1 may need to be adjusted so as to achieve the desired biologic effect. Furthermore, as discussed below, chronic administration of IGF-1 may result in changes in IGF-1 pharmacokinetics necessitating modification of the IGF-1 dosage [10].

In this short term study, the IGFBP levels did not change after the administration of a single dose of IGF-1. Repeated chronic administration of IGF-1, especially in large doses, is associated with a fall in IGFBP-3 levels [24]. This is mediated indirectly through an IGF-1 induced fall in growth hormone [25]. Studying patients with advanced CRF, Miller et al [10] observed a fall in serum IGFBP-3 levels after prolonged use of IGF-1. This change

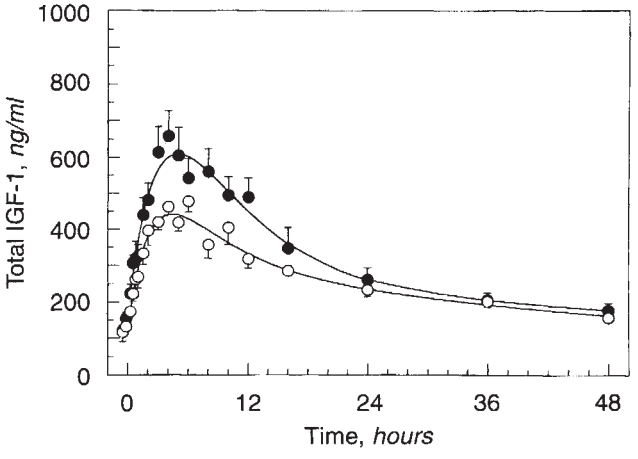

Fig. 5. *Serum total IGF-1 levels before and after the administration of 80 μg/kg IGF-1 s.c. to six normal (○) and six CRF (●) subjects.*

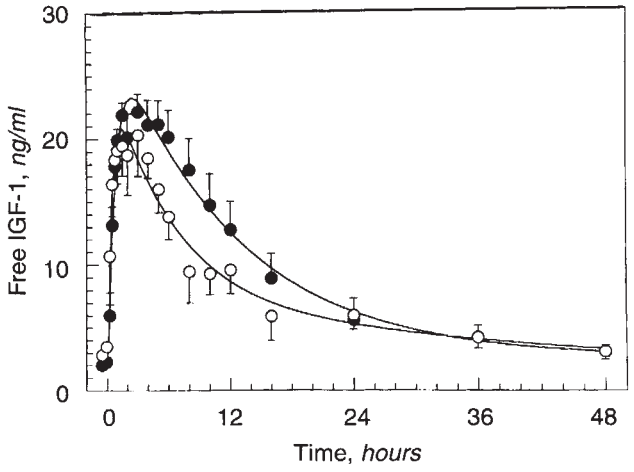

Fig. 6. *Serum free IGF-1 levels over time in the same subjects receiving IGF-1 as in Figure 5.* Note the different scales for free and total IGF-1 levels. Symbols are: (●) CRF patients; (○) normal.

in IGFBP-3 levels may affect IGF-1 pharmacokinetics and increase IGF-1 bioavailability. Higher free IGF-1 levels following IGF-1 administration could conceivably lead to an increase in untoward side effects or possibly to increasing resistance to IGF-1 action due to receptor down-regulation. These possibilities must be considered when planning long term IGF-1 administration [10, 25].

Despite resistance to IGF-1 action in uremia, this hormone may have an important role in the treatment of patients with CRF. First, IGF-1 has growth promoting and anabolic properties, and its administration to rats with CRF results in increased body weight and growth [26]. In humans with end-stage renal disease on dialysis, IGF-1 treatment lowers plasma amino acid and glucose levels [9]. These anabolic properties suggest that IGF-1 may be of value in treating CRF patients with malnutrition and muscle wasting. Studies at this center and elsewhere are also underway exploring the renal function promoting properties of IGF-1. Miller et al [10] have provided preliminary evidence showing that short term administration of IGF-1 can improve renal function in patients with advanced CRF.

Fouque, Peng and Kopple [27] recently reported the findings of their study of serum total IGF-1 pharmacokinetics in patients with end-stage renal disease on maintenance hemodialysis or peritoneal dialysis. As in our study with predialysis patients, they found that the total serum IGF-1 MCR did not differ significantly from that measured in normal controls. The volume of serum total IGF-1 distribution was reduced, and the C_{max} was increased. While they did not measure IGFBP levels, they postulated that the higher C_{max} was likely due to an increase in serum IGFBPs. Our finding that CRF subjects have elevated serum IGFBP levels and a high total IGF-1 C_{max} substantiates this hypothesis. In this same study they noted that the serum total IGF-1 half-life (but not the MCR) was accelerated when their subjects received IGF-1 in a dose of 100 μg/kg, but not when they were given a dose of 50 μg/kg. We saw no difference in serum total IGF-1 half-life in CRF patients who received 80 μg/kg per day. Fouque et al [27] suggested that the shorter total IGF-1 half-life might reflect IGF-1 binding to IGFBPs that are cleared more readily from the circulation. If this were true, then the MCR would have been faster. However, in peritoneal dialysis patients the MCR was essentially the same as in normal controls; in hemodialysis patients the MCR, while on average higher, did not differ significantly from controls. Accordingly, we suggest that the accelerated half-life reflects constant clearance from a smaller volume of distribution. As in this study of pre-end-stage renal failure patients they found that the estimated IGF-1 production rate was unaltered in patients requiring dialysis.

It is well established that the kidney is a major site of clearance of small protein hormones including insulin and proinsulin [8]. On the other hand, little is known about the renal or the extrarenal clearance of IGF-1. In part this is due to the difficulty in measuring IGF-1 clearance, since IGF-1 is tightly complexed to circulating IGFBPs and escapes very slowly out of the circulation. Indeed, IGF-1 half-life is measured in hours whereas the half-life for insulin is measured in minutes. Distribution studies in animals show that after an i.v. injection, IGF-1 reaches a higher concentration in the kidney than in any other organ [28]. Nevertheless, the true role of the kidney in IGF-1 clearance and metabolism is still unclear. The present study and that of Fouque [27] showing that advanced chronic renal failure does not affect IGF-1 metabolic clearance suggests that the kidney may not be an important organ in IGF-1 disposal. On the other hand, it is conceivable that other uremia-induced changes, such as increased skeletal muscle receptor number [23], may increase extrarenal removal and compensate for any reduction in renal clearance.

It has been stated that release of IGF-1 from IGFBPs is achieved in part through proteolytic cleavage of the IGFBP, which then results in reduced affinity for IGF-1 [3]. In some conditions, such as pregnancy, trauma, and type II diabetes, serum protease activity is increased [3, 4, 29] and in some patients with chronic renal disease urinary IGFBP-3 protease activity is also increased [30]. Our observation of increased levels of immunoreactive IGFBP-3 fragments in CRF serum raised the possibility of increased IGFBP-3 protease activity. However, measured protease activity was not increased. Accordingly, we conclude that the increase in IGFBP-3 fragment production reflects reduced renal clearance.

In summary, we have shown that unlike the closely related protein hormone insulin, the pharmacokinetics of IGF-1 is largely unaltered in advanced chronic renal failure. We attribute this difference from other protein hormones to the presence of serum IGF binding proteins which restrict the passage of IGF-1 out of the circulation and thus profoundly affect IGF-1 clearance. In CRF, elevated serum IGFBP levels reduce the total IGF-1 volume of distribution and this results in an increase in the maximum total serum IGF-1 levels following acute administration of the hormone. In contrast, serum free IGF-1 levels rise to levels comparable to that seen in normal subjects.

Acknowledgments

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Reprint requests to Ralph Rabkin, M.D., Veterans Affairs Medical Center (154L), 3801 Miranda Avenue, Palo Alto, California 94304, USA.

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